The Archives of Internal Medicine

Vol. XVI NOVEMBER, 1915 No. 5

CARBOHYDRATE UTILIZATION IN DIABETES

BASED ON STUDIES OF THE RESPIRATION, URINE AND BLOOD *

ELLIOTT P. JOSLIN, M.D.

BOSTON

In the classical work of Naunyn[1] on diabetes mellitus occurs the following passage: "In general, even in severe diabetes, at least in man, the carbohydrates ingested are not completely excreted in the urine again as sugar. A portion of the starch, as well as of the dextrose, will be burned in the organism." This view was also shared by Kulz. Naunyn, however, refers to a case in which von Mering records an excretion of all the sugar ingested, and attention is called in the report of the cases of Kulz to four instances in which apparently a similar condition existed.

Von Noorden[2] defines diabetes as "a disease in which the capability of the organism adequately to burn grape sugar is pathologically lowered," and in another place[3] he says: "One cannot help thinking that, in man, even when death has resulted from coma, the diabetes has not always been 'quite complete'—that is to say, the pathological processes which produce diabetes have not developed so far, and the factors which favor the storing up of glycogen have not been so completely destroyed as is the case in a dog whose pancreas has been entirely ablated."

Notwithstanding all the work on diabetes, this question of the utilization of carbohydrates in human diabetes has not been settled. In diabetic dogs evidence has accumulated pointing to the complete loss

* Submitted for publication April 27, 1915.

* From the Nutrition Laboratory of the Carnegie Institution of Washington, Boston.

* I wish to acknowledge my grateful appreciation of the help received from Mr. Emmes, Miss Babcock, Miss Tompkins, Miss Corson and Miss Sandiford of the Nutrition Laboratory, as also my indebtedness to Mr. Higgins, who controlled several of the experiments with the Tissot apparatus, and to my secretary, Miss Helen Leonard, for cheerful work on long computations and puzzling charts.

1. Naunyn: Der Diabetes Melitus, 1906, p. 173.
2. Von Noorden: Zuckerkrankheit, Ed. 6, 1912, p. 2.
3. Von Noorden: Metabolism and Practical Medicine, 1907, iii, 542.

of this power to utilize carbohydrate, and the work of Murlin and Cramer[4] has given definite results on this point, although so recent a writer as Landsberg,[5] working from a different point of view with other animals, comes to the opposite conclusion. The present paper is concerned with diabetes in man and I wish to call attention to certain observations bearing on this problem which are related to the body weight, the urine, the storage of carbohydrate in the body, the respiratory metabolism of diabetics both fasting and following the administration of food and the remarkable disappearance of acidosis in diabetics with prolonged fasting, which is associated with a rise in their respiratory quotient.

I. THE INFLUENCE OF WEIGHT ON THE DETERMINATION OF THE UTILIZATION OF CARBOHYDRATES IN DIABETES

The changes in weight which occur in a normal individual, following a slight increase of the carbohydrate in the diet, are so striking that one might hastily conclude that a study of the weights of a diabetic patient would give some idea as to his utilization of starch and sugar. A closer scrutiny of the problem, however, reveals many difficulties. In the first place, the diet employed in most cases of diabetes and all severe cases, is low in carbohydrates, and seldom reaches 10 per cent. of that of normal individuals. In other words, it amounts to less than 50 gm. carbohydrate—200 calories—per day. The effect of 200 calories on the weight is possible of determination theoretically, but practically such an experiment is difficult because the protein, fat and carbohydrate must be kept at uniform levels for a long period. But in a severe case of diabetes some of even this small amount is lost in the urine, which renders the available carbohydrate for increasing the weight still less. There are other complications. In a severe case of diabetes, the patient with 50 gm. of carbohydrate in the diet, usually excretes more than 50 gm. of sugar in the urine, and it is difficult to assign in proper proportion this excess of urinary sugar between the carbohydrate ingested and the carbohydrate already stored in the body on the one hand, and the protein simultaneously ingested and the body protein on the other.

Remarkable changes in the weight of normal as well as of diabetic patients will also occur, although the caloric value of the diet remains constant, if the proportion of fat to carbohydrate is altered. A diet rich in carbohydrate brings about an increase in weight, whereas a diet of exactly the same number of calories, although chiefly made up of fat, lowers the weight. These changes undoubtedly are due simply

4. Murlin and Cramer: Jour. Biol. Chem., 1913, xv, 365.
5. Landsberg: Deutsch. Arch. f. klin. Med., 1914, cxv, 465.

to the retention of water by the tissues on a carbohydrate diet, and loss of water on a fat diet. Such changes appear reasonable because the storage of 1 gm. of carbohydrate in the body demands the retention of 3 gm. of water, 1 gm. of protein requires the storage of 0.75 gm. of water, and 1 gm. of fat requires only 0.1 gm. of water. These changes are well illustrated[6] by Table 1.

TABLE 1.—Changes in Weight Under Fat and Carbohydrate Diets

Date	Food and Drink			Body Weight kilos	Gain (+) or Loss (—) gm.
	Solid Matter gm.	Water gm.	Total gm.		
Carbohydrate Diet					
4/16/04	...	....	.....	75.086	.....
4/16-17/04	970	3,577	4,547	75.443	+ 357
4/17-18/04	966	3,553	4,519	75.414	— 29
4/18-19/04	966	3,491	4,457	75.269	— 145
Fat Diet					
4/19-20/04	750	3,108	3,859	74.319	— 950
4/20-21/04	745	4,150	4,896	73.480	— 839
4/21-22/04	747	4,152	4,899	72.528	— 952

Average gain per day, carbohydrate diet, + 61 gm.
Average loss per day, fat diet, — 914 gm.
Water stored per day, carbohydrate period, + 165 gm.
Water lost per day, fat period, — 906 gm.

It is important for the clinician to bear this in mind, because it explains the rapid change in weight which often follows the initial diminution of the carbohydrate in the diet of diabetic patients and its replacement with fat.

An increase in weight following a marked increase of carbohydrate in the diet is strikingly illustrated in severe diabetic patients under the oatmeal treatment.[7] Under these conditions the weight may rise 4.5 kg. in one or two days. Undoubtedly you all have seen edema during the course of an oatmeal cure. It is significant that some of these cases show little or no carbohydrate in the urine. I cannot give proof that patients showing this increase in weight fail to give evidence of burning more than a trifling amount of carbohydrate, but from other similar cases I suspect this often to be the case. This point deserves further study. I think, however, that there will be general agreement that the gain in weight following the sudden introduction of large quantities of carbohydrate is accounted for by the storage—temporarily, perhaps—of carbohydrate in the body. That this storage or delay of excretion is accentuated in the presence of diseased kidneys

6. Benedict and Joslin: A Study of Metabolism in Severe Diabetes, Carnegie Institute of Washington, 1912, Pub. No. 176, p. 93.
7. Mirowsky: Deutsch. med. Wchnschr., 1912, xxxviii, 459.

is common knowledge. Barrenscheen[8] showed that milk sugar excretion was delayed on the day following an oatmeal cure.

The administration of sodium bicarbonate is frequently followed by a gain in weight. Thus,[9] in Case 220, the changes in weight during the administration of sodium bicarbonate were as shown in Table 2.

TABLE 2.—CHANGES IN WEIGHT DURING THE ADMINISTRATION OF SODIUM BICARBONATE

Date	Sodium Bicarbonate gm.	Body Weight kilos.	Date	Sodium Bicarbonate gm.	Body Weight kilos.
11/2	0	48.1	11/ 7	20	50.7
11/3	0	48.6	11/ 8	20	51.5
11/4	0	49.0	11/ 9	20	52.4
11/5	0	48.6	11/10	20	53.3
11/6	20	49.3	11/11	20	53.3

In order to show that this gain in weight was not directly due to the alkali, but rather to retention of salt, the weights of another diabetic patient, Case 135, were taken while on a salt-free diet[10] (Table 3).

TABLE 3.—CHANGES IN WEIGHT ON A SALT-FREE DIET

	Intake						Urine								
Date, 1908	$NaHCO_3$ Gm.	Carb., Gm.	Protein, Gm.	Fat, Gm.	Alcohol, Gm.	Liquids c.c.	Vol., c.c.	N, Gm.	NH_3, Gm.	Acetone and Diacetic Acid., Gm.	Beta-oxy. Acid, Gm.	P_2O_5, Gm.	Cl., Gm.	Sugar, Gm.	Wt., Lbs.
1/26	0	135	110	185	..	3,500	3,720	21.8	4.2	7.9	29	4.4	8.2	160	88¼
1/27	0	135	110	185	..	3,500	3,940	19.6	4.3	7.8	29	4.5	6.3	165	89¼
1/28	0	135	110	185	..	3,500	3,210	20.5	4.4	7.3	24	4.6	5.9	160	86¾
1/29	0	135	90	155	..	3,500	3,210	19.2	4.1	7.3	26	4.2	4.8	163	85¾
1/30	25	135	70	185	..	3,500	3,190	16.3	3.5	8.7	23	4.1	1.6	145	85
1/31	25	120	60	95	23	5,370	4,600	19.1	4.3	12.6	51	5.1	2.3	146	83¼
2/1	37	120	100	120	45	5,250	4,050	18.7	3.3	10.7	39	4.3	2.0	137	82¼
2/2	52	70	60	95	45	5,370	3,510	16.0	3.5	10.2	37	3.9	2.1	121	81¾
2/3	..	15	15	30	45	800	260	15.0	....	....	..	....	....	86	....

It will be seen that while on the salt-free diet the weight steadily fell, and despite the administration of sodium bicarbonate later, no increase in weight occurred. This observation has been elsewhere confirmed. I might here make the clinical observation that a salt-free diet in diabetes is inadvisable. It is also interesting that I have never

8. Barrenscheen: Biochem. Ztschr., 1912, xxxix, 232.
9. Benedict and Joslin: Loc. cit. (Note 6) p. 94.
10. Joslin and Goodall: Jour. Am. Med. Assn., 1908, li, 727.

seen the death from diabetic coma of a diabetic patient who had dropsy, nor have I encountered such in the literature.

The simple enumeration of these various facts affecting the weight shows how complicated is the determination of the utilization of carbohydrate from it alone. Changes in weight, however, do afford, when combined with other methods of clinical investigation, new fields for work.

The changes in weight which a healthy fasting man undergoes at the beginning of a fast are known. The fasting man at the Nutrition Laboratory lost 2,850 gm. in three days, and consumed during these three days body substance equivalent to 161 gm. of protein, 149 gm. of carbohydrate and 407 gm. of fat. It is possible that from a series of observations on diabetic patients similarly fasted, conclusions of value as to the storage of carbohydrate in the body might be secured. Ten of my patients who were available for this purpose showed on an initial fast a loss of weight considerably less, and occasionally a gain in weight was recorded. Following the termination of the fast, although very little food was given, an increase in weight out of proportion to the amount of food given was almost invariably observed.

In one case no mineral waters or alkalies were taken, and yet gain in weight occurred during fasting. It is not unexpected that the gain in weight was often coincident with a fall in the excretion of urine. A gain in weight during fasting raises the question as to whether new carbohydrate has not been formed in the body, and as a result of its formation water retained. This line of investigation deserves attention. It will be referred to later in the discussion of severe cases of diabetes treated by prolonged fasting, the method which Dr. F. M. Allen[11] has had the courage to introduce and has so accurately defined that it is safe for any practitioner to employ.

II. THE UTILIZATION OF CARBOHYDRATES BASED ON INTAKE IN DIET AND OUTGO IN URINE

The comparison between the carbohydrate ingested and the sugar excreted in the urine is the common method of determining the utilization of carbohydrates. It would appear to be a simple procedure, but, as a matter of fact, the problem is far more difficult than has heretofore been considered. Your attention is first directed to the possibilities of error in reckoning the carbohydrate in the diet. Most severe diabetics under careful observation live on diets low in carbohydrate, seldom in excess of 50 gm. Therefore errors of 5 gm. in the estimation of

11. Allen: Jour. Am. Med. Assn., 1914, lxiii, 939; Boston Med. and Surg. Jour., 1915, clxxv, 241.

carbohydrates, though actually small, are proportionately large. It is seldom that the actual quantity of carbohydrate in the diet has been analyzed. In many of the cases food has not even been carefully weighed, and approximate portions of food have been supposed to contain definite quantities of carbohydrate. Take, for example, cream: The quantity of carbohydrate contained in half a pint may vary 5 gm., making an error of 10 per cent., if the total carbohydrate for the day amounted to 50 gm., or 20 per cent. if limited to 25 grams.

Vegetables constitute a considerable proportion of the diet of these patients with severe diabetes. Often in the literature—and I plead guilty to the charge—the quantity of carbohydrate in the mixture of vegetables chosen from those containing less than 10 per cent. carbohydrate for the day, has been roughly estimated. Recently I have taken more careful account of the amount of vegatables eaten, and it has come out that the quantity of vegetables prescribed and eaten frequently varies from 300 gm. to 1,000 gm. Any accurate computation, therefore, of a carbohydrate balance must be based not alone on the total quantity of vegetables eaten in the day, but on the actual quantity of each vegetable, even in these low carbohydrate groups. Furthermore, varieties of the same vegetable vary in percentage of carbohydrate. It makes a difference of 5 gm. in a day whether 500 gm. vegetables contain 1 per cent. more or less of carbohydrate. But this is not all. Analyses of carbohydrate in vegetables include the cellulose contained in them as well as the starch and sugar. How much shall we subtract from our total carbohydrate intake on account of this undigested cellulose which is lost in the feces?

The other foods commonly used in the study of the metabolism of diabetic patients are potato, oatmeal, bread, fruit. The potato, oatmeal and bread are usually carefully weighed, and the analyses of these foods are fairly constant, but the percentage of carbohydrate is so large that I should not dare to be positive about the quantity of carbohydrate which my patient received unless standard varieties of these foods were employed. With fruit frequent errors exist, because usually an orange or grapefruit is allowed and seldom the actual weights of the portions eaten are determined. A further error occurs in that the intake of carbohydrate is reckoned indifferently as starch or sugar. As a matter of fact, 100 gm. of starch when converted to sugar amount to 105 gm. Errors of 5 and 10 gm. a day in computing the carbohydrate intake may easily occur and in a period of a week form notable amounts, from 35 to 70 gm. Physiologists and physicians must not take too seriously clinical statements about the carbohydrate in the diet, and greater accuracy must be employed in the future. We need, first, a standard test diabetic diet, and, second, we need to

employ it for at least five days. Unfortunately, even at the end of this time the results may be unsatisfactory, because the condition of the patient's tolerance may have changed in this period either for better or worse.

The estimation of sugar in the urine is far more accurate than that of the carbohydrate in the diet, provided the analysis is made in one of our best laboratories, but I would hesitate to accept as final in accurate computations many routine analyses made in private practice or in hospitals. Too often the method employed in the estimation of the sugar is not mentioned, and I suspect many results are obtained with the polariscope which may involve an error of 20 gm. or more, owing to the presence of levorotary bodies. Urinary analyses, however, are usually far and away ahead in accuracy of that observed in the collection and measurement of the urines of diabetic patients. The admirable methods adopted in the ward of the Russell Sage Institute at Bellevue Hospital and at the Rockefeller Hospital have been seldom followed by experimenters in the past. I pass over errors of forgetfulness or design on the part of the patients, as regards both diet and collection of urine. Dogs may not be any more honest, but we do not expose them to temptation or trust their memory. How often a patient states that a trifling amount of urine has been lost at stool! I realize this is trite, but a good share of the arguments based on the utilization of carbohydrate rests on data which are not above reproach.

The variability of excretion of urine and urinary constituents from day to day is another source of error. If the diet is not constant the variation may be great. In one of our tests designed to determine the utilization of levulose, during seven days prior to the administration of levulose the average volume of urine was 1,079 c.c. On the day the levulose was given the volume of urine was 966 c.c., the next day 390 c.c., and on the following day it amounted to 1,175 c.c.; it then returned to near the average quantity. Yet the habits of this patient's daily life were nearly constant, and except for the one levulose day changes in the diet were not extreme. Such marked variations in the volume of the urine on successive days must be reckoned with, because with such great changes in volumes of urine, the quantities of the constituents of the urine change too, though to a much less extent. In this same case, the average daily excretion of nitrogen for the fifty-five days which included this period was 7.3 gm., but on the day when 81 gm. levulose were given with very little other food, it fell to 6.53 gm. and on the next day to 4.34 gm. This low point was never reached by this same patient on a fasting day, and the quantity of levulose is considerably less than would be supposed to exert so strong a positive action, particularly when delayed or diminished oxidation

is taken into consideration. Consult Table 4 and also chart of variations in excretion of urine and sugar of a severe diabetic on a constant diet, shown further on.

TABLE 4.—EFFECT OF LEVULOSE

Case 785. Male, aged 17. Weight, 42 Kilos.

Output					Intake				
Vol., c.c.	Diac. Acid	Sugar, Gm.	Nitrogen, Gm.	Ammonia, Gm.	Carb., Gm.	Prot., Gm.	Fat, Gm.	Alcohol, Gm.	Calories
1,079*	+	11.1†	7.83	....	17	58	127	9	1,506
966	+	7	6.03	0.69	90‡	21	30±	3	735
890	++	5	4.94	0.25	20	63	110	9	1,385
1,175	+	3	8.25	0.74	20±	63	110±	9	1,385±

* Average for previous seven days.
† None on six days.
‡ Levulose, 81 gm. Carb. in Diet 9 ± gm. in the form of vegetables.

Experiments designed to test the utilization of carbohydrate should be conducted on patients who are in equilibrium both as regards weight and urinary excretion.

III. THE IMPORTANCE AS WELL AS THE INFLUENCE OF CARBOHYDRATE STORED IN THE BODY ON THE UTILIZATION OF CARBOHYDRATE INGESTED

It is well known that following a period of fasting large quantities of carbohydrate can be administered without subsequently appearing in the urine. The best illustration of this is von Noorden's oatmeal treatment. Thus Case R. of the Benedict and Joslin series[12] showed a positive carbohydrate balance of 520 gm. during an oatmeal cure, although he never after this cure became sugar-free save for occasional days, despite rigorous dieting. A more spectacular demonstration is the severe diabetic of Klemperer,[13] who took 100 gm. of glucose in divided portions during twenty-four hours without more than a few grams appearing in the urine. Almost as striking is that of a boy of 17 (Case 785) who came to me in the twentieth month of the disease. By consulting Table 4 it will be seen that only 7 gm. of sugar appeared in the urine following an intake at one time of 81 gm. levulose, although by observations before and after the tolerance was known to be low. A summary of his metabolism is given in Table 5.

12. Benedict and Joslin: Loc. cit. (Note 6) p. 57.
13. Klemperer: Therap. d. Gegenw., 1911, lii, 447.

TABLE 5.—SUMMARY OF METABOLISM IN CASE SHOWN IN TABLE 4*

Case 785. Severe diabetes. Weight, 42 kilos. Male. Age at onset, 15. Duration since onset twenty months.

Period	Nitrogen Balance		Carbohydrate Balance	
	Urine and Feces	Diet	Urine	Diet
55 days	440.	407.	190.	919.
Daily average	8.0	7.0	3.5	16.7
Daily average	8.9	Sugar present in urine 20 days		15.4
		7.8	8.8	
Daily average	7.5	Sugar absent from urine 32 days		15.1
		6.4	0.0	

* Nitrogen in feces estimated at 10 per cent. of nitrogen in diet.

During the fifty-five days he was under my observation the average daily nitrogen in the diet was estimated at 7.0 gm., and in the urine and feces 8.0 gm. The carbohydrate in the diet was 16.7 gm. and in the urine 3.5 gm. During thirty-two of the fifty-five days, sugar was absent from the urine and on twenty days it was present, although the average daily carbohydrate in the diet was the same. A study of Table 5 would suggest this being due to the slightly lower nitrogen intake on the sugar-free days. This is not quite justifiable, because another factor enters in—namely, starvation—for on several of the thirty-two days the patient received no food at all. These starvation days evidently played an important rôle. How very important is shown by the test already recorded in Table 4, where 81 gm. of levulose were administered and only 7 gm. carbohydrate appeared in the urine.

Is it possible for the body to store so large a quantity of carbohydrate as 520 or even more grams? Furthermore in what form may it be retained in diabetic patients?

Nearly all experiments on the utilization of carbohydrates in the past have been based on the difference between the carbohydrate intake and the carbohydrate excreted. Unless the amount of the carbohydrate stored in the body is known, it is unjustifiable to say that the carbohydrate excreted represents a part of that ingested during the same twenty-four hours. All data in reference to the D:N ratio are confused by the possibility of stored carbohydrate. The importance of the storage of carbohydrate thus becomes evident.

The influence of carbohydrate so stored in the body is also great. Whatever virtue the oatmeal cure possesses, all agree that it depends

in major part on preceding starvation, which has tended to exhaust the carbohydrate depots of the body.

Glycogen.—Carbohydrate is stored in the body in various ways but most of it is supposed to be in the form of glycogen, and this is about equally divided between the liver and the muscles. An old estimate of Bunge that the body had 400 gm. is roughly approximated by experiments on fasting men and professional athletes doing severe work without food. This figure may be taken as a fair average, but there are enormous variations. This statement is based on glycogen which has been shown to be burned; it does not exclude the possibility of some glycogen still remaining in the body, and in fact Benedict says: "It would appear that the estimate of 400 gm. of glycogen for the content of the body is if anything too small rather than too large." Experiments on fasting men show that they may burn from 93 to 232 gm. in the first three days.[14, 15] In diabetic patients the quantity of glycogen is universally considered to be far below this amount, but Frerichs[16] found, on puncturing the liver of two diabetics, a small amount of glycogen in one and a considerable amount in the other, and Kulz[17] found from 10 to 12 gm. glycogen in the liver of a diabetic who had been for a long time on a diabetic diet. Examinations of the tissue removed from the livers of living diabetic patients show appreciable quantities of glycogen, and it is the experience of pathologists that the organs of diabetic patients contain more than traces of glycogen. It is most unfortunate that no data exist which enable us to determine what this minimum is. It is quite conceivable that although it might be extremely small at any one moment, a small quantity might be frequently formed and destroyed, and the sum of these small quantities reach a substantial amount in twenty-four hours.

The recent work of Helly[18] throws new light on the problem. He points out the striking contrast between the constant presence of glycogen in the liver of human diabetes and the very small quantity which is found in the severe diabetes of depancreatized dogs, yet even in the latter the power of the liver to form or deposit glycogen is shown when levulose is administered. If a milder form of diabetes is produced in the dog more glycogen remains in the body and there is a closer resemblance to human diabetes; whereas with total removal of the pancreas there was only 0.065 per cent. of glycogen in the liver.

14. Benedict: The Influence of Inanition on Metabolism, Carnegie Institute of Washington, 1907, Pub. 77, p. 464.
15. Benedict: A Study of Prolonged Fasting, Carnegie Institute of Washington, 1915, Pub. 203, p. 251.
16. Frerichs: Ueber den Diabetes, p. 272; cited by Nehring and Schmoll (Note 34).
17. Kulz: Arch. f. d. ges. Physiol. (Pflüger's), 1876, xiii, 267.
18. Helly: Ztschr. f. exper. Path. u. Therap., 1914, xv, 464.

On the other hand, with partial removal, even though there be 8 to 10 per cent. of sugar in the urine, there was 0.3 per cent. of glycogen. By microscopic examination so considerable a quantity as this appeared small.

Blood Sugar.—Sugar is also stored in the body in the form of blood sugar. The normal quantity of sugar in the blood of healthy individuals varies between 0.07 and 0.11 per cent. and for convenience in calculations may be considered 0.1 per cent. This rises quickly after a meal rich in carbohydrates, but soon falls to its former level. In fifty-five observations on fifteen of our diabetic patients the percentage of blood sugar varied from 0.12 to 0.36 per cent. But the blood of these diabetic patients does not behave like that of normal individuals following the ingestion of food. It is true that the percentage of sugar rapidly increases following a carbohydrate meal, but it does not as rapidly fall, and in my own experience most diabetic patients, even after prolonged fasting, show values for blood sugar which are far above normal. Certain types of diabetic patients—namely, those with disease of the kidneys—are especially prone to maintain high percentages of sugar in the blood for many days after their urines have become sugar-free. It is impracticable to consider that the percentage of blood sugar is maintained independently of the other tissues in the body—first, because the percentage is so unstable; second, because there is no constant relation between the sugar in the blood serum and the sugar in the total blood, and third, because the capacity of the blood for storage of sugar is so slight. If we assume an individual of 70 kilos body weight and consider that 7 per cent. of the weight is made up of blood, we have 4.9 kilos of blood with a normal sugar content of 0.1 per cent. This would amount to 4.9 gm., even taking the highest for the normal individual, and should we take the highest figures we have encountered even after the administration of food with our diabetic patients, namely 0.36 per cent., the total quantity of sugar stored in the blood would not be far from 18 gm.—a trifle more than a half ounce.

Falta[19] has called attention to the slow return of the blood of diabetic patients to its former sugar level, and emphasizes this point as of fundamental importance in diabetes. He points out that the disturbance of blood sugar utilization is not the same as the disturbance of glycogen formation for the blood sugar regulation may be interfered with when the glycogen formation is not.

Kleiner and Meltzer[20] have also beautifully shown this same difference in depancreatized dogs. Whereas, following the injection of

19. Falta: Med. Klin., 1914, x, 9.
20. Kleiner and Meltzer: Proc. Soc. for Exper. Biol. and Med., 1914, xii, 58.

4 gm. dextrose per kilo weight, the sugar in the blood of normal dogs increases fourfold—namely, from 0.20 per cent., to 0.79 per cent.—and that of depancreatized dogs threefold—from 0.38 per cent. before to 1.19 per cent. after the injection—the blood sugar of the former returned nearly to normal at the end of an hour and a half, while the diabetic dogs even then showed 0.86. It is significant that in these experiments the quantities of sugar excreted in the urine were practically the same. Interesting as these figures are from this point of view, from another they are still more interesting. It is impossible to account for all the sugar ingested by adding together the sugar found in the blood and that in the urine. Where did the sugar go? You may say it was burned, and this possibility, though not probability, must be admitted in the normal animal, but no one would contend this to be wholly the case in the depancreatized animal.

At the Nutrition Laboratory we have been able to carry these experiments to their logical conclusion, for we have had the opportunity to determine the respiratory quotient following the administration of levulose to severe diabetics. In Table 20 will be found a report of the effect of levulose when administered to severe diabetic patients in amounts to 2.51 gm., 2.42 gm. and 1.95 gm. per kilogram body weight. In the first and third cases there was no increase in the respiratory quotient. A considerable portion of the levulose was probably excreted in the first case, but in the third little or none. The explanation of this difference in behavior in the storage of levulose is probably that the first patient had not fasted beforehand and that the third had been on a low carbohydrate diet for a long time; this is confirmed by the second case, in which also little of the levulose was excreted when administered following a period of strict dieting. An increase in the respiratory quotient occurred in this case, but it was so slight as to preclude any considerable quantity of the sugar having been burned. It should also be recorded that in all the cases the levulose was given at one time and not spread out through the twenty-four hours, as in Klemperer's test. This gives added emphasis to the possibility of the presence of an empty storehouse for carbohydrate in the body. I also have evidence that the gradual administration of carbohydrates is of little value, provided the body is not prepared to retain it. Following etherization a patient (Case 808), while fasting for the first twenty-four hours was sugar-free, but on the next day, although only 2 gm. carbohydrate per hour were administered, he excreted practically all of it, although formerly his tolerance amounted to 50 gm. carbohydrate.

The small amount of glycogen and the still smaller quantity of blood sugar represent an amount of carbohydrate far too low to

account for the phenomena above described in diabetes. Other sources for storage of sugar in the body must be sought, as has been emphasized by Ivar Bang. If we should assume that the percentage of sugar in the blood was the same for all the fluid in the body, certain amounts of sugar might be stored in this manner. While such an assumption is not wholly justifiable, it has some basis, for we know that sugar exists in the spinal fluid of diabetics, as well as in other fluids. In normals Dr. Jacobson tells me that he has not found it so closely to follow the blood, but the opposite was true in his cases of diabetes mellitus. It gets into the blood and cannot seem to get out. Notable percentages of sugar, not very different from those in the blood, have been found in pleuritic and ascitic fluids, and Husband found even 0.7 per cent. in the amniotic fluid. There is some doubt about its presence in sweat, but we do have a record of sweet tears. Yet granted that the assumption is correct, we cannot increase our storage capacity very much that way. For example, assuming the total quantity of fluid in the body as 60 per cent. of the body weight of 70 kg., we have 42 kg. of body fluid, from which we must deduct 4.9 kg. already reckoned as blood. This leaves us a remainder of 37.1 kg. of fluid in the body, and using the highest figure—0.36 per cent.—for blood sugar which we have encountered, the quantity of sugar in this mass of fluid would be only 133 gm. This is not enough relatively to explain Kleiner's and Meltzer's experiment.

Another source for the formation, although perhaps not for the storage of carbohydrate in the body, has long been recognized in protein. The close connection which is maintained between protein and carbohydrate in diabetes would make a clinician with modest chemical knowledge seek for some combination of carbohydrate in the protein molecule—some arrangement by which a portion of the sugar molecule could be stored in protein or given up as occasion arises, just as water is squeezed out of a sponge. Good chemists, and I have asked many, assure me that even with glucoproteins sugar can be extracted from the protein molecule only when the molecule itself is disintegrated. The large quantity of movable protein and fat in the body suggests a large carbohydrate reservoir, too. Few realize how large this quantity of movable protein is. It has been shown by Albert Müller[21] that by overfeeding, 210 gm. of nitrogen, the equivalent of 1260 gm. of body protein, in turn the equivalent of 6.3 kilos of muscle tissue, can be retained by the body, and conversely, it has been shown by Benedict[15] that even more—277 gm.—can be removed. This movable protein amounts to about one-third of the total body protein. The readiness

21. Müller: Zentralbl. f. d. Ges. Physiol. u. Path. d. Stoffswechs., 1911, vi, 617.

with which fat can be increased and decreased in the body is universally recognized.

Although we are not allowed to say that carbohydrate can be extracted from the protein molecule, leaving it intact, we do know that in severe diabetes sugar can be formed out of protein. Professor Lusk[22] has demonstrated this in completely depancreatized dogs and in his now famous diabetic patient, 3.65 gm. dextrose appeared in the urine for each gram of nitrogen therein contained. This represents approximately 60 gm. dextrose for each 100 gm. protein. If we should assume that in diabetic patients there were 1,200 gm. movable protein, this would furnish a possible source of 720 gm. more of carbohydrate.

Unfortunately one cannot be sure that in the disintegration of the protein molecule the nitrogen and carbohydrate leave the body hand in hand. As a rule, the nitrogen loiters behind, greatly to our annoyance in estimating the source of the sugar in the urine. Mendel and Lewis[23] have recently shown that this delay was increased if either indigestible substances or cotton seed oil form a prominent part of the diet—just the sort of foods which our diabetic patients eat. Consequently if an attempt to determine the quantity of carbohydrate from protein (dextrose nitrogen ratio D : N) is made, this irregularity in the excretion of nitrogen must be considered. When one adds to this difficulty that of determining what share the quantity of residual carbohydrate in the body bears to the total sugar excreted, and when one considers that even under an absolutely uniform diet of 1,000 gm. meat and 1,750 c.c. fluid intake for fifteen days Naunyn[24] found variation of sugar excretion from 12 gm. to 43 gm., and frequently of 100 per cent., I feel very modest about asserting that my patients are producing any given quantity of sugar for each gram of nitrogen excreted. Naunyn says that these spontaneous variations may reach even 70 gm. Kulz has emphasized this same point. If under ideal conditions for fifteen days such variations exist, it behooves one to accept with caution reported D : N ratios for a period of a few days as being of value or to base arguments, as is sometimes done, on the D : N ratio of single isolated days selected from a series. In the tables of Rumpf, Allard, Hesse, and some of Lüthje's, D : N ratios are recorded which Professor Lusk and I would feel indicated a far larger per cent. of carbohydrate coming from protein than is actually the case. It is arbitrary selection to pick from these tables all ratios above 3.65 : 1 and say they are wrong and to class the remainder as correct. It is

22. Mandel and Lusk: Deutsch. Arch. f. klin. Med., 1904, lxxxi, 472.
23. Mendel and Lewis: Jour. Biol. Chem., 1913-14, xvi, pp. 19, 37.
24. Naunyn: Des Diabetes Melitus, 1906, p. 183.

furthermore remarkable that with fasting all D:N ratios cease to exist. It is also hard to understood how a patient one day fails to burn the protein of an ox, but the next day burns his own body protein with ease. Fasting diabetics will afford unusual opportunities to study this point. As a rule, the high D:N ratios are found when the nitrogen excretion is high, and it may be that to produce these high ratios large quantities of protein may be required.

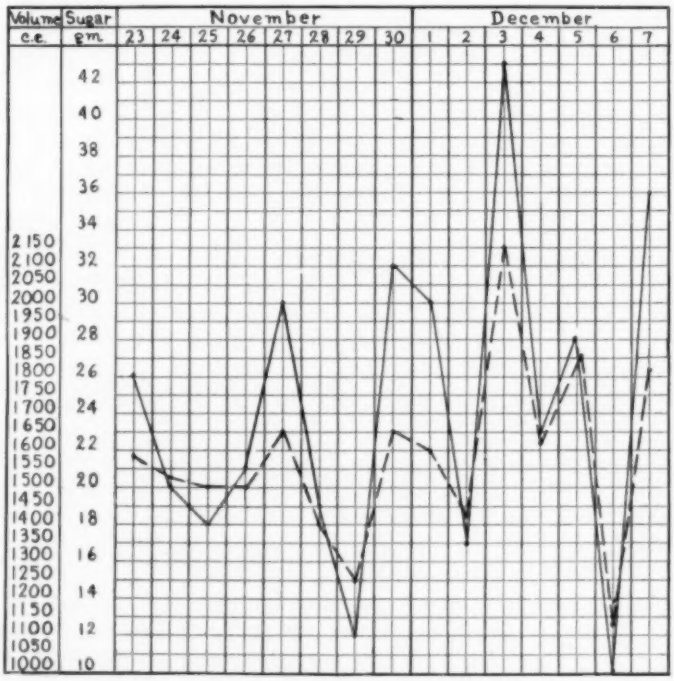


Chart illustrating variations in excretions of urine and sugar of a severe diabetic on a constant diet (from Naunyn). Diet constant 1,000 gm. meat, 1,750 c.c. fluid. Line composed of dots and dashes indicates c.c. urine in twenty-four hours; continuous line, gm. sugar in twenty-four hours.

The small part which the blood plays in the storage of carbohydrate has been pointed out. This is peculiarly unfortunate because one would hope from the percentage of sugar in the blood to derive some knowledge of the course of metabolism in diabetes. As if to emphasize the independence of the metabolism to the content of sugar in the body, I submit at this point Table 6, which gives the respiratory quotients obtained upon individuals whose blood sugar was deter-

mined at the time of the test, reserving discussion of the same to a later portion of the paper.

TABLE 6.—The Blood Sugar and Respiratory Quotient in Severe Diabetes

Case No.	Condition	Per cent. of Sugar in Blood	R. Q.
806	Fasting	0.12	0.71
806	Fasting	0.14	0.68
786	Fasting	0.17	0.69
806	After potato (60 gm. carb.)	0.18	0.69
765	Fasting	0.18	0.74
810	Fasting	0.19	0.72
806	After one egg and 200 gm. vegetables	0.19	0.72
765	Fasting	0.23	0.76
765	Fasting	0.24	0.73
714	Fasting	0.25	0.78
786	After oatmeal (60 gm. carb.)	0.25	0.74
765	After oatmeal (10 gm. carb.) and potato (48 gm. carb.).	0.26	0.74
773	Fasting	0.27	0.70
773	After oatmeal (80 gm. carb.)	0.30	0.70
746	Fasting	0.30	0.70
746	After oatmeal (40-60 gm. carb.)	0.36	0.74
786	After oatmeal (120 ± gm. carb.)	0.36	0.83

IV. THE RESPIRATORY METABOLISM AND ITS RELATION TO THE UTILIZATION OF CARBOHYDRATE

An examination of the composition of the carbohydrate molecule will show that it contains sufficient oxygen to unite with all the hydrogen present. Consequently, for each volume of oxygen used in the oxidation of carbohydrate a volume of carbon dioxid will be produced. The relation which the volume of carbon dioxid produced bears to the oxygen required for the oxidation of a food constitutes its respiratory quotient. It is obvious, therefore, that the respiratory quotient of such a carbohydrate as glucose ($C_6H_{12}O_6$) is 1. It matters not whether the oxidation takes place rapidly outside of the body in a flame, or less obtrusively in the body during twenty-four hours. Protein, on the other hand, does not contain sufficient oxygen for the hydrogen atoms contained in its molecule. As a result, in the burning of protein, oxygen must be used not only for the carbon in the molecule, but for the hydrogen as well. The denominator of the fraction is thus increased, and the respiratory quotient of protein must be less than 1, and is 0.81. The protein molecule is made up of many component parts and while the respiratory quotients of these parts vary greatly, yet for protein as a whole the foregoing quotient, 0.81, holds. With fat a similar condition exists to that in protein, only there is still more hydrogen present to require oxygen, so that the amount of oxygen necessary for the combustion of fat is still greater, and as a result the respiratory quotient falls to 0.70. The respiratory quotient of alcohol is still lower, namely, 0.67. Beta-oxybutyric acid, which can be taken

as the chief one of the group of acid bodies formed in diabetes, has a respiratory quotient of 0.89, diacetic acid has a respiratory quotient of 1.00, and acetone of 0.75, so that one will not go far astray to take 0.89 as a common respiratory quotient for these three acid bodies.

The respiratory quotient of an individual can be determined by measurement of the quantity of carbon dioxid exhaled and the oxygen absorbed. When this is done, information is obtained concerning the character and total amount of the combustion taking place in the body. Since the urinary nitrogen gives us a definite idea of the quantity of protein metabolized, if we calculate what this represents and subtract it from the total material burned, we have left the combustion derived simply from fat and carbohydrate. When the respiratory quotient of fat and carbohydrate, as well as that of the individual, is known, it is possible, by computation, to determine the share which these two variables have taken in the total metabolism.

TABLE 7.—THE RESPIRATORY QUOTIENT (R. Q.) OF A FOOD IS OBTAINED BY DIVIDING THE VOLUME OF CARBON DIOXID PRODUCED DURING ITS OXIDIZATION BY THE VOLUME OF OXYGEN ABSORBED

VOLUME OF OXYGEN ABSORBED	R. Q.
Carbohydrate: $C_6H_{12}O_6 + 6\ O_2 = 6\ CO_2 + 6\ H_2O$	
Oxygen is required for oxidation of carbon alone	
$\frac{6\ CO_2 \text{ produced}}{6\ O_2 \text{ absorbed}} =$	1.00
Fat: $C_{51}H_{102}O_6$	
Oxygen required for carbon and a large quantity of hydrogen	0.71
Protein: Occupies an intermediate position	0.81
Alcohol: C_2H_6O	0.67
Beta-Oxybutyric acid: $C_4H_8O_3$	0.89
Diacetic acid: $C_4H_6O_3$	1.00
Acetone: C_3H_6O	0.75

The Technic of the Determination of the Exchange of Carbon Dioxid and Oxygen in Man.—Two types of apparatus are employed to learn the exchange of carbon dioxid and oxygen in man; the calorimeter and respiration apparatus. In the closed chamber of the calorimeter the oxygen admitted and the carbon dioxid withdrawn can be accurately determined in periods usually of one hour's duration, but it is better to take the average of the results obtained in three successive periods. Occasionally each period may be shortened to three-quarters of an hour, exceptionally to half an hour, but the large size of the calorimeter increases the chances for error. The calorimeter is cumbersome, expensive to construct and to maintain, and the length of the experiment is not only disagreeable to the patient, but disadvantageous in studying the results of rapid changes in the metabolism, which are desirable in a study of the utilization of foods. On the other hand, the respiratory apparatus is advantageous because the exchange

of gases can be determined during short periods of fifteen minutes. It is disadvantageous, however, because, the periods being so short, errors at the beginning and end of the periods are magnified and because the individual must breathe through a nosepiece or mouthpiece, and this introduces an abnormal state. Unfortunately, in each form of apparatus, the error of a leak falls chiefly on the oxygen, because the patient and the apparatus constitute a closed circuit, and any diminution in gas in this circuit must be offset by the addition of oxygen. A more troublesome source of error and one difficult to avoid arises from the possibility of the patient exhaling carbon dioxid, which has previously accumulated in the body, at a more rapid rate than corresponds with the oxygen inhaled. The patient is said to "pump out" carbon dioxid. There is also another error due to carbon dioxid which is lost by cutaneous respiration, and it has been calculated that this would lower the quotient 0.01 to 0.15.

Many pitfalls, therefore, lurk in the determination of the respiratory exchange of an individual. The carbon dioxid is the more easily estimated of the two gases and in early experiments on metabolism investigators attempted this alone. The determination of oxygen is far more difficult. Hence, in dealing with the respiratory quotient, which depends on the relation of these two determinations to each other, one treads on very dangerous ground, and all statements regarding the respiratory quotient of individuals must be accepted with caution. The general picture of the respiratory quotient in an individual is far more valuable as a guide to his true metabolism if based on several experiments than is the result of a single experiment. Similarly, it is probably safer to average the results of a series of cases than to attach too much importance to figures obtained in one.

The Respiratory Quotient of the Normal Individual.—The respiratory quotient of the normal individual is best determined at least twelve hours after a meal. It has been shown that if this rule is not followed the composition of the meal will have a marked influence on the result. Under these circumstances the respiratory quotient of normal individuals does not greatly vary. Benedict, Emmes, Roth and Smith[25] working at the Nutrition Laboratory of the Carnegie Institution, have studied the basal gaseous metabolism for 89 men and 68 women and their average results are shown in Table 8.

I would call attention to the slight difference existing between the respiratory quotient of men and women—0.83 and 0.81. I have also incorporated the heat production, calculated from the oxygen intake, which was approximately 25 calories per kilogram per twenty-four hours. This latter figure is lower than we are apt to consider, but it

25. Benedict, Emmes, Roth and Smith: Jour. Biol. Chem., 1914, 18, 139.

should be remembered that it is based on fasting periods when the patient is purposely endeavoring to be quiet. It would be absolutely wrong, from such determinations covering periods of fifteen minutes, or even a few hours, to draw conclusions on the total heat production for the day. In illustration of the method and at the same time of the difficulties of determining the respiratory quotient of normal individuals I give the figures in my own case (Table 9).

TABLE 8.—RESPIRATORY QUOTIENT AND TOTAL METABOLISM OF NORMAL INDIVIDUALS AT REST AT LEAST TWELVE HOURS AFTER THE LAST MEAL

Individuals	R. Q.	Calories per Kilo per 24 Hours
89 men	Average = 0.83	25.5
68 women	Average = 0.81	24.9

TABLE 9.—RESPIRATORY QUOTIENT OF A NORMAL PERSON

Normal individual (E. P. J.) fasting experiment. December 23, 1914. Weight, 64.9 kilos. Height, 177.8 centimeters.

Duration		CO_2 Per Min. c.c.	O_2 Per Min. c.c.	R. Q.	Calories per kilo. per 24 hours
Min.	Sec.				
15	6	152	192	0.80	20.40
14	59	150	194	0.77	20.51
15	0	153	196	0.78	20.77

Average = 0.78

Naturally I took the greatest possible pains to be quiet and breathe in a normal manner, but it will be seen that whereas the values for the carbon dioxid of themselves, and of oxygen for themselves vary to an extremely small degree from period to period, yet they differ sufficiently to make a considerable variation in the respiratory quotient. This experiment emphasizes the possibilities for error in the determination of the respiratory quotient even under most favorable circumstances.

The respiratory quotient of individuals fasting for long periods is well exemplified by the studies made by Benedict[15] on a man who went thirty-one days without food. These are illustrated in Tables 10 and 11.

It will be seen that, prior to the experiment, the respiratory quotient differed little from that of the group of normal individuals above mentioned. With the withdrawal of all food the respiratory quotient fell, and after the fifth day reached a point which Magnus-Levy[26] has said

26. Magnus-Levy: Ztschr. f. klin. Med., 1905, lvi, 83.

theoretically represents the quotient which is obtained when the metabolism consists of 85 per cent. of fat and 15 per cent. of protein, namely, 0.72. In other words, five days of starvation removed the last discernible influence of carbohydrate remaining stored in the body, and the individual lived wholly on body fat and body protein. It is possible to discover how much fat and how much carbohydrate take part in the metabolism.

TABLE 10.—THE RESPIRATORY QUOTIENT OF A MAN DURING A PROLONGED FAST

Period	Time	R. Q.	Calories per Kilogram Body Weight
Preliminary Period	Fourth day before fast	0.81	33
	Third day before fast	0.89	32
	Second day before fast	0.89	29
	First day before fast	0.82	27
Period of Fast	Days 1—5 of fast	0.77 (Avge.)	26
	Days 6—31 of fast	0.72 (Avge.)	23
	Days 6—31, early a. m.	0.73 (Avge.)	23
After Period	Second day after breaking fast*	0.78	25
	Third day after breaking fast*	0.94	27

* Twelve hours after food.

TABLE 11.—QUANTITIES OF PROTEIN, CARBOHYDRATE AND FAT OXIDIZED BY FASTING MAN AT NUTRITION LABORATORY *

Period of Fast	R. Q.		Quantities Oxidized			Calories per kilo. per 24 hours
	Actual	Non-Prot.	Protein gm.	Carb. gm.	Fat gm.	
1st Day	0.78	0.76	43	69	135	30
2d Day	0.75	0.74	50	42	142	30
3d Day	0.74	0.74	68	39	130	29
4th Day	0.75	0.71	71	4	136	28
5th Day	0.76	0.72	63	15	133	28
6th to 31st Day Average	0.72	0.70	53	0†	114	26

* Determined from the Daily Metabolism, the Urinary Nitrogen and the Calculated Non-Protein R. Q.
† Actually a total of 32 gm. carb. were burned during the sixth to thirteenth day, inclusive, and later none.

Knowing the nitrogen in the urine, one can calculate the amount of oxygen employed by the body for the oxidation of the protein[27] which it represents, and correspondingly, the amount of carbon dioxid given off can be determined. If we subtract these computed figures from the total carbon dioxid and oxygen obtained by direct experiment, we have left the carbon dioxid produced by the non-protein metabolism in the body, and the relation of the two gives the non-protein respira-

27. In estimating the quantity of body protein burned from nitrogen in the urine the equivalent 6.00 is employed instead of 6.25.

tory quotient. In a useful table constructed by Lusk,[28] the percentage of carbohydrate and of fat for any given non-protein respiratory quotient between 70 and 100 can be calculated. On this basis it was shown that Benedict's fasting man burned either no carbohydrate or only a trace after the sixth day. When the respiratory quotient of this man was 0.73 on the seventh day it represented a nonprotein respiratory quotient of 0.70 and no carbohydrate was burned. A respiratory quotient of 0.74 gave a nonprotein respiratory quotient of 0.71, which represents the oxidation of 3.8 gm. of carbohydrate; a respiratory quotient of 0.76 gave a nonprotein respiratory quotient of 0.72, which is evidence that 15 gm. carbohydrate were burned.

Respiratory Quotient in Normal Individuals after Food.—The respiratory quotient following the ingestion of food is shown well by the fasting man at the Nutrition Laboratory for the periods before fasting commenced. It will be seen that twelve hours after food it varied from 0.81 to 0.89 in the four days. Similarly, following the termination of the fast, the respiratory quotient rose, indicating the combustion of large quantities of carbohydrate.

An experiment was performed on myself which was comparable to those later carried on with the diabetic patients when tests were made of the influence of food on their metabolism. The changes in my own respiratory quotient following the ingestion of 60 gm. of carbohydrate in the form of oatmeal are given in Table 12.

It will be seen that the respiratory quotient within an hour rose some eight points after eating 60 gm. of carbohydrate in the form of oatmeal. It has been calculated that if 48 gm. carbohydrate are burned in twenty-four hours at the rate of 2 gm. of carbohydrate each hour continuously for the twenty-four hours, the respiratory quotient would rise 3 points—in other words, would be about 0.75 instead of 0.72, which is a fat-protein quotient. I wish to emphasize the change in respiratory quotient of only 3 points when approximately 48 gm. carbohydrate are burned at the rate of 2 gm. carbohydrate per hour per day, and the rise of 8 points following directly on the ingestion of 60 gm. carbohydrate. The continuous combustion of small portions of carbohydrate amounts to the combustion of a considerable quantity of carbohydrate during the whole day, and yet it will raise the respiratory quotient very little. The combustion of 24 gm. of carbohydrate at the rate of 1 gm. per hour could scarcely be detected with our present methods, and yet a tolerance for 24 gm. carbohydrate is relatively a high tolerance when one is dealing with serious cases of diabetes.

The Respiratory Quotient in Diabetes.—In mild cases of diabetes, when the urine is free from sugar and the carbohydrate in the diet

28. Williams, Riche and Lusk: Jour. Biol. Chem., 1912, xii, 357.

large, the respiratory quotient differs little from that of normal individuals. The respiratory quotient of these same mild cases of diabetes will be lowered by fasting or by the withdrawal of carbohydrate, as just shown in the case of the normal fasting man. Undoubtedly the limited quantity of carbohydrate in the diet in cases of severe diabetes is responsible to a large degree for the low respiratory quotient which such patients show. Magnus-Levy called attention to this, and so

TABLE 12.—METABOLISM OF A NORMAL INDIVIDUAL AFTER FOOD
Weight, 64.9 kilos. Height, 177.8 cm.

Date	Condition	CO_2 Per Min. c.c.	O_2 Per Min. c.c.	R. Q.	Calories Per Kilo. Per 24 Hours
9/ 9/14	1-2 hours after breakfast	205	241	0.85	26
9/10/14	1-2 hours after breakfast	192	237	0.81	25
9/30/14	9 a. m., fasting	159	194	0.82	21
	10:30 a. m., after 60 gm. carb. as oatmeal	189	212	0.90	23
12/23/14	8 a. m., fasting	152	194	0.78	21
	1 p. m., fasting	151	196	0.77	21

TABLE 13.—ILLUSTRATION OF FALL IN RESPIRATORY QUOTIENT OF MILD DIABETIC *
Case 714. Female. Aged 38 years, 9 months. Weight 53 kilos.

Date	R. Q.	Urine Sugar	Diet †			
			Carb. gm.	Prot. gm.	Fat gm.	Alcohol gm.
Dec. 3	....	4.4%	+ +	+ +	+ +	0
Dec. 4- 5	....	20 gm. ‡	+	+	+	10
Dec. 5- 6	0.78	0	0	0	0	25
Dec. 6- 7	0.75	0	15	40	45	10
Dec. 7- 8	0.75	0	15	45	60	7
Dec. 10-11	0.73	0	15	55	100	9

* Tests were made fasting at 8 a. m., which was one hour after the collection of the twenty-four-hour urine.
† Approximate.
‡ In fourteen hours.

have other observers. It is well exemplified by the change in the respiratory quotient in Case 714. This patient, with only moderate acidosis, became sugar-free on April 16, 1914, following fourteen days of treatment. On Dec. 3, 1914, she reentered the hospital with 4.4 per cent. of sugar, but under fasting treatment became sugar-free after the omission of four meals. The respiratory quotient on successive days is shown in Table 13.

It will be seen that whereas the respiratory quotient was 0.78 on entrance, owing undoubtedly to the oxidation of some of the carbo-

hydrate ingested, though much at the same time was being lost in the urine, this rapidly decreased to 0.73 under starvation followed by a low carbohydrate diet. Yet this could not be considered a severe case of diabetes. The quotient was low simply because the woman was living almost exclusively on a fat protein diet.

The problem of drawing inferences from the respiratory quotient in diabetes is complicated by the fact that much of even the little carbohydrate which is given to a diabetic patient is lost in the urine. The patient really approaches the condition of the fasting man in that he is living exclusively on fat and protein, although in this case not that of his own body. If all the carbohydrate ingested is lost in the urine, his respiratory quotient would be 0.72. But there are other complications. Occasionally cases of diabetes are seen in which the sugar in the urine exceeds that of the diet, and speculation at once arises as to the source of this excess of sugar. Magnus-Levy[26] has pointed out that if the sugar in the urine amounted to 60 gm. and the protein in the diet to 100 gm., the additional quantity of oxygen which would be demanded to form this amount of sugar out of protein would lower the respiratory quotient to 0.70. The situation is still further complicated by the presence of unoxidized acid bodies in the urine, amounting frequently to 20 to 40 gm. and occasionally to 60 gm. calculated as beta-oxybutyric acid. The amount of oxygen consumed in the formation of these bodies—for beta-oxybutyric acid is far richer in oxygen than are protein and fat—would again lower the quotient, and it has been calculated by Magnus-Levy that the respiratory quotient of a diabetic patient presenting 60 gm. of sugar in the urine for 100 gm. of protein in the diet, and excreting 20 gm. of beta-oxybutyric acid, would fall as low as 0.69. For convenience, these figures are summarized. The respiratory quotient of the fasting man at the Nutrition Laboratory was 0.72. The calculated respiratory quotient of a normal individual who is burning 15 per cent. protein and 85 per cent. fat is 0.72. The theoretical respiratory quotient of a diabetic individual excreting all the carbohydrate in the diet, and 60 gm. of glucose for each 100 gm. of protein in the diet, is 0.70. The theoretical respiratory quotient of the diabetic individual excreting 60 gm. glucose for 100 gm. protein and 20 gm. beta-oxybutyric acid as well, is 0.69. These calculations presuppose that the sugar and beta-oxybutyric acid excreted were formed during the same twenty-four hours, but who knows whether this is the case? The theoretical nonprotein respiratory quotient of a case of diabetes living on fat and the noncarbohydrate part of the protein molecule, as calculated by Lusk, is also 0.69.

Table 14 shows the theoretical respiratory quotient, which should be reached under varying conditions of diet for a normal individual,

and the changes which theoretically are present under special conditions in diabetes. Figures of this type have dominated the discussions of the metabolism in diabetes from the start, and whenever experiments have not produced figures comparable with these, they have often been considered erroneous. We are taught to believe that cases of diabetes are not severe unless the respiratory quotient is 0.69. It is questionable, however, whether the experimental data at our disposal enable us to say that our theories are backed up by the results which we obtain. If one looks over the lists of respiratory quotients obtained in successive periods with any variety of respiratory apparatus or calorimeter, he will be shocked at the discrepancy and forced to the belief that any argument based on a change in the respiratory quotient of one point is unjustifiable, and that any argument which is based on a change in the respiratory quotient of two points really hangs on a

TABLE 14.—THEORETICAL RESPIRATORY QUOTIENTS (FROM MAGNUS-LEVY)

Diet	Calories	R. Q.
Protein, 100 gm. (100 × 4.1 = 410) Carb., 567 gm. (567 × 4.1 = 2325)	2,735	0.97
Protein, 100 gm. (100 × 4.1 = 410) Fat, 250 gm. (250 × 9.3 = 2325)	2,735	0.72
Loss in Urine Sugar, 60 gm. (60 × 4.1 = 246)	2,489	0.70
Loss in Urine Sugar, 60 gm. (60 × 4.1 = 246) B-Oxy. acid, 20 gm. (20 × 4.7 = 94) Total loss = 340	2,395	0.69

very slender thread. A change of three points is, however, deserving of consideration, but modesty should rule in conclusions which are to be drawn from any given set of experiments.

It is appropriate to discuss here what constitutes a severe diabetes. At the outset it can be said for our own encouragement that Naunyn did not pretend to be able to distinguish accurately between the various types. Usually by severe diabetes is understood those cases in which —to quote von Noorden—"notwithsanding a prolonged, extreme carbohydrate-free diet, the urine contains sugar." By an extreme carbohydrate-free diet von Noorden undoubtedly meant one containing protein, fat and a few green vegetables—in other words, a diet with 10 gm. carbohydrate, more or less—not a strictly fat-protein diet. The definition is also open to objection, because one frequently meets with cases of diabetes of long duration in which but a small per cent. of the carbohydrate intake is excreted in the urine, yet this persists for many days on an extreme carbohydrate-free diet, but the case could not be classed as severe.

Another method of classification is adopted by Lusk, who considers cases severe in which, when the patients are put on a protein-fat diet, there is a dextrose-nitrogen ratio of 3.65:1. By this he means that 3.65 gm. of dextrose appear in the urine for 1 gm. of nitrogen, or the 6 gm. of protein which it represents. In other words, 60 per cent. (actually 3.65÷6.25=58.4 per cent.) of the protein burned by the body appears in the urine in the form of sugar. Lusk considers that this is the greatest possible amount of sugar which can appear in the urine on a carbohydrate-free diet, and he assumes that it comes wholly from protein. This conclusion has been reached with many observations on dogs, following injections of phloridzin, and by one case of diabetes coming under his personal observation, and he refers to other cases selected from the literature.

Unfortunately, or perhaps fortunately, neither of these methods of classification at the present time are wholly satisfactory, because, thanks to Dr. Allen, our patients now become sugar-free very readily. It is possible that fasting will not remove the sugar from the urine of all diabetic patients, but this has been my experience with every case when I have followed Dr. Allen's directions, and my experience coincides with that of many others. It may be that recent cases of diabetes have been of a different type from those hitherto encountered, but this is hardly possible. Consequently we cannot adopt the definition of von Noorden, and it is embarrasing to adopt the precise definition of Lusk. The dextrose-nitrogen ratio vanishes with fasting, and the clinician does not wish to expose his patient before beginning fasting to the dangers of a protein-fat diet simply to determine the severity of his case. I am hoping that with the added knowledge of diabetes which the introduction of fasting has brought about, Professor Lusk will pursue his studies further and give us definite rules for testing the severity of the disease. Perhaps definite quantities of protein alone or some special form of protein or derivative of protein could be administered to these patients, and the amount of sugar in the urine determined. Should this method not furnish satisfactory results, another series could be carried out in which varying quantities of fat as well as protein could be added, and if a third factor were necessary, the calories per kilo could be standardized. But we can trust Professor Lusk to give us help. Of course dextrose-nitrogen ratios are of little significance without simultaneous reports of the blood sugar.

In the data which will follow, consideration will be taken of both von Noorden's and Lusk's classification, but also the severity of the cases will be indicated by a statement of the time intervening between the period of observation and death in coma. It would seem as if the severity of the type of diabetes which resulted in death by coma should challenge criticism.

As the periods of observation before death in coma are of importance, the intervals between the determination of the respiratory quotient of the patient and death are given. See Table 16, which will later be discussed more in detail. This appears far more rational than to give the duration of the course of the disease, for many patients present a mild type of diabetes for many years, changing over to a severe type at a comparatively short period before death.

Table 15 summarizes the respiratory quotients of cases of diabetes considered severe by their observers:

TABLE 15.—RESPIRATORY QUOTIENT IN SEVERE DIABETES

Year	Observers	Cases	R. Q.
1894	Weintraud and Laves: Ztschr. f. physiol. Chem., 1894, xix, 603.	1	0.70
1897	Nehring-Schmoll: Ztschr. f. klin. Med., 1897, xiii, 39.	2	0.72
1905	Magnus-Levy: Ztschr. f. klin. Med., 1905, lvi, 86.	2	0.71
1907	Mohr: Ztschr. f. exper. Path. u. Therap., 1907, iv, 910.	1	0.72
1908-1911	Benedict and Joslin: Carnegie Inst. of Washington, Publications 136 and 176, 1910, 1912.	19	0.73
1912	Rolly: Deutsch. Arch. f. klin. Med., 1912, cv, 494.	8	0.74
1912	Grafe and Wolf: Deutsch. Arch. f. klin. Med., 1912, cvii, 201.	3	0.74
1912-1914	Benedict and Joslin, 1914-15.....	7	0.73
		Total 43	Average 0.73

It will be seen that there is surprising unanimity of agreement among the different groups. It should be stated that Leimdorfer[29] has obtained much lower quotients varying between 0.64 and 0.68 with five cases which he considered severe. His figures, however, have not been generally accepted. One of the cases which he considered mild at no time showed a respiratory quotient above 0.70. According to the computations given above from Magnus-Levy, it was shown that, theoretically, in a diabetic patient with 60 gm. of sugar in the urine for each 100 gm. of protein in the diet—in other words, approximately the Lusk dextrose-nitrogen ratio—and with 20 gm. of beta-oxybutyric acid, the respiratory quotient would not go below 0.69, and he further points out that, in order for the ratio to sink to 0.653, 150 gm. of sugar must be formed from 150 gm. of protein, and 40 gm. of beta-oxybutyric acid must appear in the urine when the patient is on a diet of 150 gm. protein and 250 gm. fat. A respiratory quotient of 0.653 is a figure so low that it should be entertained with scepticism. The average respiratory quotient of 0.73 for forty-three cases of diabetes clinically considered severe is a far safer figure to follow than

29. Leimdorfer: Bio-Chem. Ztschr., 1912, xl, 326.

to pick out one, two or three from the forty-three cases and say that these represent severe cases of diabetes and the others do not. The errors of the determinations of the quotients are so great that the average figures are safer than the individual ones. These respiratory quotients, as Grafe and Wolf[30] pointed out, show that at least some carbohydrates were being oxidized by severe diabetic patients. They also pointed out that with the improvement of patients the respiratory quotients increased from 0.743 to 0.817 in a fasting condition.

These figures suggest at the first glance that very little carbohydrate was burned in this group of severe cases of diabetes. The respiratory quotients are identical with the quotients obtained under similar conditions with the fasting man at the Nutrition Laboratory, though his average for the whole day for the fasting period was 0.72. But we must remember that two corrections are to be made in these figures; first, sugar has been lost in the urine which has been formed from protein, and second, there have been varying amounts of beta-oxybutyric acid, diacetic acid and acetone excreted. Both of these processes represent processes of oxidation and by demanding additional oxygen for which no carbon dioxid is produced tend to lower the respiratory quotient. Therefore, if we grant that the series represents cases of severe diabetes, we must reach the conclusion that these diabetic patients utilized some carbohydrate, and that their respiratory quotients would have been several points above 0.73, had they not been lowered to 0.73 by the production of sugar from protein and the formation of acid bodies.

Are the cases reported in Table 15 severe? At least no cases of greater severity have been hitherto published. By von Noorden's criterion they might be considered severe, for they did not become sugar-free with restricted diet, yet it is true that this restricted diet was not so rigid as is often employed on account of the marked acidosis. If we accept Lusk's criterion (and I am not ready to do so until a second human case is studied under modern conditions[31]) they were not severe. Not one of Benedict's and my cases showed a persistent D:N ratio of 3.65:1. Yet the clinical facts point to severity. In the first group of nineteen cases of diabetes reported in 1908-1912 by Benedict and myself, eighteen patients are dead and of these fifteen

30. Grafe and Wolf: Deutsch. Arch. f. klin. Med., 1912, cvii, 201.

31. By modern conditions I mean (1) exclusive fat-protein diet, (2) under surroundings which make errors in diet impossible, (3) a duration of at least seven days to exclude the washing out of stored carbohydrate, (4) a constant (not falling) D:N ratio of 3.65:1 for the last three of the seven days, and (5) several daily blood sugar determinations to furnish some proof, inadequate though it be, that the sugar in the urine has not come from that left over in the blood. At present I cannot advocate such a test because of the danger of acidosis, and believe it better to leave the question in this form, undecided.

died in coma. This fact can be taken as a measure of their severity. I do not believe, however, that this alone justified us in saying that a case of diabetes is of the severest type. I conceive it possible, for a moderately severe case of diabetes, by sudden changes of diet, to be driven into coma accidentally. This was done years ago, when diabetic patients who were living on a free diet on coming to the hospital were suddenly deprived of carbohydrate and the fat and protein were increased. It appears to me quite probable that most cases of coma in diabetes have occurred long before the disease had reached its greatest severity, and I wish to point out that therein lies great hope for the future.

It will be of interest, however, to note the respiratory quotient of a group of six cases of diabetes all ending in coma, death occurring within a period of 44 to 14 days from the time of observation, and to compare these with a group of patients whose respiratory quotient was observed at a greater interval from death by coma. This is shown by Table 16.

TABLE 16.—Respiratory Quotient in Severe Diabetes: Comparison of Fatal Cases and Cases of Living Patients

Fatal Cases			Living Patients		
No. of Cases	Days Before Coma	R. Q.	Case No.	Days Before* March 1, '15	R. Q.
6	44-14	0.71	552	801	0.72
8	442-70	0.74	765	125	0.73
			786	111	0.71
			806	72	0.70
			4 Cases	801-72	0.715

* All of these patients were in good condition May 1, 1915, which would add sixty-two days to the duration since the observations were made.

A consideration of this table suggests that with approaching death the respiratory quotient falls. It will be seen that the cases ending fatally within a period of from 44 to 14 days from the time of observation, gave a quotient of 0.71, as contrasted with a quotient of 0.74 in cases terminating fatally in coma at an interval from death of from 442 to 70 days. If we had these figures alone, the inference might be justified, but caution is necessary before drawing such a conclusion. Four living diabetic patients show a respiratory quotient almost as low—0.715. Instead of progression toward death by coma, their general condition has improved. In other words, a falling respiratory quotient does not necessarily mean approaching death by coma. It does mean that these patients have lived for prolonged periods on an almost exclusively fat-protein diet and suggests that they are forming carbohydrate out of protein and producing acid bodies.

It should be said that all of these living patients have been treated either by much restricted diets or by fasting as advocated by Dr. Allen. When they were first seen the cases appeared to be quite as severe as those earlier studied which ended fatally in coma. What shall we say of them at present? None of these patients can be considered well, but all lead a comfortable life at home.

The group of patients dying within a period of from forty-four to fourteen days deserves further comment. The average quotient of these cases was 0.71. From four of these the non-protein respiratory quotient has been reckoned, and it amounted to 0.695. This respiratory quotient implies that much material must have been formed in the course of the metabolism which used a portion of the oxygen. This was especially true of Case 246, in which there was a respiratory quotient of 0.69, which was based on an average of twenty-nine periods, most of which were fasting.[32] Stimulated by inquiries from Professor Lusk, I am fortunately able to show the cause of the particularly low quotient in this patient. His diet and urinary analyses will be found in Tables 17 and 18. The average daily urinary nitrogen for the six days of observation was 16.6 gm., and it was considered that this represented approximately the metabolism of 100 gm. protein. The beta-oxybutyric acid was 46.6 gm. daily and allowing for acetone and diacetic acid the total excretion of acid bodies was assumed to be 60 gm. The fat in the diet as originally recorded was probably inaccurate, and I believe 165 gm. daily near to the exact quantity. From these tables it will be seen that the daily carbohydrate in the diet was 71 gm., and the dextrose excreted was 102 gm. giving a minus balance of 31 gm. This, with the 16.6 gm. nitrogen in the urine, gives a D : N ration of only 1.9 to 1. In Table 18 are placed the data from which the respiratory quotient can be calculated from the diet and urine, and they show that after deductions for dextrose and acetone bodies, the theoretical quotient would be 0.692, which it will be remembered was identical with the respiratory quotient found by experiment. These tables are submitted as proof that a quotient of 0.69 does not necessarily mean that the capacity for burning carbohydrate has been totally abolished.

Computations of a similar character by Grafe and Wolf[30] lead to the same conclusion.

According to these writers, "the conception which on the whole appears to have the greatest probability is that even the severest diabetic has at his disposal 20 to 30 gm. of glycogen for combustion or synthesis, thirteen to twenty hours after a meal containing a minimal

32. Benedict and Joslin: Metabolism in Diabetes, Pub. Carnegie Institution of Washington, 1910, No. 136, p. 68.

amount of carbohydrate. Perhaps the complete loss of the power of combustion of sugar is, broadly speaking, no longer consistent with life."

TABLE 17.—METABOLISM IN A CASE OF SEVERE DIABETES WITH A RESPIRATORY QUOTIENT OF 0.69 *

Case C., No. 246. Male. Acute onset at 28. Death in coma in fifteen months.

Day	Urine					Diet				Sodium Bicarb. Gm.
	Volume, c.c.	N, Gm.	NH_3 Gm.	B-oxy., Gm.	Dextrose, Gm.	Carb., Gm.	Prot., Gm.	Fat, Gm.	Alcohol, Gm.	
1	2,935	16.3	4.8	29	72	15	13	65	15	0
2	3,710	13.3	5.0	34	106	98	22	225	30	0
3	4,370	19.6	5.5	61	134	65	100	200	30	60
4	4,085	19.4	5.4	61	107	65	100	200	30	60
5	3,230	14.7	5.6	46	100	125	45	100	30	25
6	2,765	16.3	5.0	48	98	65	100	200	22	25
Ave.	3,601	16.6	5.2	46.6	102	71	65	165	26	28

*Daily protein metabolism estimated at 100 gm. Total acetone bodies estimated at 60 gm.
Carbohydrate in diet, 71 gm.
Dextrose in urine, 102 gm.
Carbohydrate balance, 31 gm.
D : N ratio, 1.9 : 1.0.

TABLE 18.—TO SUPPLEMENT TABLE 17 *

Case C., No. 246.

Diet	Gm.	Calories	O_2 Liters	CO_2 Liters	R. Q.
Protein	100 × 4.1 =	410	96.6	78.2	
Fat	165 × 9.3 =	1535	333.1	235.5	
Carbohydrate	71 × 4.1 =	291	58.9	58.9	
Alcohol	26 × 7 =	182	37.9	25.3	
		2418	526.5	397.9	0.756
Lost in Urine					
Dextrose	102 × 3.7 =	337	76.1	76.1	
Acetone bodies as B-oxyb.	60 × 4.5 =	243	58.1	51.6	
		620	134.2	127.7	
		1798	392.3	270.2	0.692

* The respiratory quotient found, based on an average of 29 periods, chiefly fasting was 0.69.

Effect of Food on Utilization of Carbohydrates in Severe Diabetes.—A moderate number of experiments on the effect of food on severe diabetics has been recorded, but the actual number of experiments to determine the effect of carbohydrate on the respiratory metabolism is very limited. Such experiments have been published by Leo,[33] who

33. Leo: Ztschr. f. Klin. Med., 1891, xix, 101.

considered that the respiratory quotient did increase in two cases of severe diabetes, although this was not uniformly the rule and he concludes that even in severe diabetes a part of the sugar ingested or formed in the body is utilized.

Nehring and Schmoll[34] tested the effect of carbohydrates also in two severe cases of diabetes, but were unable in either to show an increase in the respiratory quotient. Frequently a fall instead of a rise in the quotient took place. Benedict and Joslin,[35] in a series of experiments chiefly with bread and dextrose, state that "the ingestion of carbohydrate produced no very material alteration in the metabolism as a whole," and later "no evidence can be found of a combustion of carbohydrate . . ." Two years later a series of experiments with oatmeal and levulose were reported, but without comment.[36]

Rolly,[37] in a series of experiments, tested the comparative effects of oats, rye, wheat, lentils and green cornmeal on diabetic patients. Unfortunately, few of the experiments were preceded by control periods. Two of his cases he considers severe. In Case 1, at three, five and six hours after 70 gm. of oatmeal were administered, the respiratory quotient was 0.73. After 70 gm. of wheat meal it was 0.76. The respiratory quotient of his Case V after 80 gm. of oatmeal was 0.71, after 80 gm. of rye meal was 0.73, and after 80 gm. of wheat meal was 0.71. Two of his other cases were only moderately severe, and the other only a light case, and all showed an increase in the respiratory quotient after their meals reaching up to 0.83, 0.85 and 0.84 respectively. It will be noted, furthermore, that of the two severe cases, in the first the quotient following administration of wheat meal which was given after oatmeal reached 0.76.

Roth[38] records slight increase of the respiratory quotient following the administration of carbohydrate. The experiments, however, lose much of their value because of the absence of fasting controls on the day the carbohydrates were given.

Falta[19] has mentioned several experiments designed to show the effect of the oatmeal cure on the respiratory quotient. The data of the experiments are not given, but he states that with one moderately severe diabetic the respiratory quotient rose only on the third day of an oatmeal cure, in which 400 gm. had been given daily. Despite this

34. Nehring and Schmoll: Ztschr. f. klin. Med., 1897, xxxi, 59.

35. Benedict and Joslin: Loc. cit. (Note 32) p. 215.

36. Schilling: Inaug. Dissert., Leipzig, 1911, tested the effects of various meals on the respiratory quotient of one severe, one mild and two moderately severe cases of diabetes, and demonstrated no specificity for oatmeal. With the severe case the results were inconstant, but usually tended to show a slight increase in the respiratory quotient.

37. Rolly: Deutsch. Arch. f. klin. Med., 1912, cv, 494.

38. Roth: Wien. klin. Wchnschr., 1912, xlvii, 1864.

enormous quantity of oatmeal, no glycosuria was observed. It is unfortunate that I have not been able to find a later publication which was promised. He furthermore makes the interesting statement, which is so remarkable as to invite confirmation, that a similar result was encountered with a normal individual, whose carbohydrate depots had been robbed by living on a diet poor in carbohydrates for a long time. It would appear that only after these depleted carbohydrate stores were replenished, did the normal individual, like the diabetic, begin to burn carbohydrate. His results are in striking contrast to the changes in respiratory quotient which were shown by the fasting man at the Nutrition Laboratory. At the end of his fast of thirty-one days he ate food almost exclusively in the form of carbohydrate and the quotient promptly rose to 0.79 and 0.96 on the second and third days respectively, emphasizing the fact that in a mixed diet carbohydrates are burned much earlier. He further states that on a meat diet or on a diet with a moderate amount of carbohydrate the diabetic patient seldom shows a quotient above 0.74, and he also noted the fact, to which attention has been called by Nehring and Schmoll, and which is also borne out by our own series of cases, that following the administration of carbohydrate a considerable quantity of carbohydrate not only remains in the body, but the respiratory quotient remains low. Intravenous injections of sugar (30 gm.) given by Falta to severe diabetics, who had eaten 300 gm. of oatmeal for three days without glycosuria, brought about an evident glycosuria, but the respiratory quotient rose proportionately little. In the case of a severe diabetic there was no increase, but a still further lowering of the already low respiratory quotient.

The present series of experiments with foods which I have to report represent a part of the experiments on diabetics whose metabolism following the administration of food was studied at the Nutrition Laboratory since 1910.

Three experiments have been conducted with levulose. In Case 332 100 gm. of levulose were administered when the patient was fasting. This patient was a severe diabetic, weight 40 kg., in the twenty-fourth month of her illness, and died five months later. The respiratory quotient before the levulose was administered was 0.72, and following the levulose the quotient was determined in six different periods during the following three hours and showed an average of 0.69. Despite the fall in the respiratory quotient, the total metabolism increased markedly, although apparently most of the levulose was excreted in the urine. Unfortunately, it is impossible to state how much of the 120 gm. of sugar in the urine for this twenty-four hours came from the levulose and how much from carbohydrates of the preceding day.

Our records indicate that the patient was on a diet containing approximately 100 gm. of carbohydrate. This fact is of interest in comparison with the next two cases, in which also levulose was given.

TABLE 19.—Effect of Levulose on a Severe Diabetic

Case 332. Female. Aged 37 years. Weight 40 kilos.

Date	Condition	CO_2 Per Min.	O_2 Per Min.	R. Q.	Calories per Kilo. per 24 Hours
3/31/11	Fasting	c.c.	c.c.		
10:50	Fasting	151	205	0.74	35
11:23	Fasting	145	211	0.69	36
	100 gm. levulose				
12:16	.....	172	271	0.63	46
12:44	.....	184	261	0.70	44
1:30	.....	180	246	0.73	42
2:05	.....	172	235	0.73	40
2:28	.....	171	250	0.68	42
2:53	.....	166	240	0.69	40
4/2/11					
8:17	Fasting	148	199	0.75	34
8:45	Fasting	151	203	0.74	35
9:14	Fasting	154	213	0.72	36
	Oatmeal = 70 ± gm. carb., 38 gm. butter				
10:13	.....	163	234	0.70	39
10:39	.....	167	228	0.73	39
11:08	.....	177	238	0.75	40
12:12	.....	170	230	0.74	39
1:28	.....	154	206	0.75	35
2:37	.....	163	209	0.78	36

TABLE 20.—Effect of Levulose on Respiratory Quotient of Diabetic Patients

Case	Duration, Months	Month Observed	Carbohyd. Preceding Day, Gm.	Levulose, Gm.	Sugar in Urine 24 Hours, Gm.	R. Q.	
						Before	After
332	Dead 28 Alive 32	23	100±	100	120	0.72	0.69
552	32	18	30	100	3	0.72	0.76
785	23	20	20	81*	7	No increase	

*81 gm. levulose and later
9 gm. carb. as vegetables
90 gm. total.

In Case 552 also 100 gm. of levulose was administered, but this was given after a prolonged period of low carbohydrate feeding. On the day previous to the experiment the carbohydrates in the diet amounted to 30 gm. The quantity of sugar in the urine in this case during the twenty-four hours of the experiment was 3 gm. The

respiratory quotient rose 4 points, namely, from 0.72 to 0.76 after the levulose.

The third case, No. 785 (Table 20), was that of a boy, aged 16, with severe diabetes of twenty months' duration, weight 42 kg. He had been made sugar-free by prolonged fasting and had been kept on a diet low in carbohydrate and protein, as well as fat. During the twenty-four hours of the test, the urine contained but 7 gm. of sugar. Notwithstanding this fact, the respiratory quotient showed no increase, but a fall of 2 points. The actual figures are not published now, but the comparative values may be considered trustworthy. The evidence in these three cases, therefore, points to no utilization of the levulose in two of the cases. In one of these most of the levulose was probably excreted, but in the other only a negligible quantity. In the third case

TABLE 21.—Effect of Potato on Respiratory Quotient in Severe Diabetes

Case Number	Duration Months	Month Observed	Carbohydrate Intake		Sugar in Urine 24 Hours, Gm.	R. Q.	
			Preceding Day, Gm.	Test Day, Gm.		Before	After
765	7	8	15	63* 22 — 85	29	0.74	0.73
806	6	8	10	60† 6 — 66	8	0.68	0.71

* 48 gm. carb. as potato, 10 gm. carb. as oatmeal, 5 gm. carb. as cream } 63 gm. Later in day, 22 gm. carb. as potato and vegetables
Also 1 egg and 30 gm. butter.
† 60 gm. carb. as potato. Later in day, 1 egg, butter, 6 gm. carb. as vegetables.

there was an increase of three points in the respiratory quotient, indicating a slight utilization of the levulose and there was no excretion of levulose of account.

It was possible to determine the effect of the administration of potato in two cases. In the first case the experiment was complicated in that the patient was given a small quantity of oatmeal at the start, which, however, was stopped on account of her dislike to it, and potato was substituted. In this case, No. 765, no change in the respiratory quotient took place, but in the second, Case 806, a slight increase was noted, and apparently rather more than would be accounted for by the limits of error.

Eleven experiments have been carried out on cases of severe diabetes with oatmeal. These were arranged in some cases to determine the immediate effect of the administration of oatmeal, and in other cases to determine the effect of the prolonged administration of

TABLE 22.—Effect of Potato on the Respiratory Quotient of a Severe Case of Diabetes

Case 806. Male. Weight 62 kilos.

Date 12/22/14	Condition	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.	Cals. per Kilo per 24 Hrs.	Blood Sugar Per Cent.
9:25		156	223	0.70	24	
9:54	Fasting.....	150	224	0.67 0.68	24 24	
10:22		155	228	0.68	25	
10:45	.....	...	...	.....	.....	0.14
	Potato = 60 gm. carb.					
10:55	.....	...	...	.....	.....	0.18
11:50	.....	181	257	0.71	28	
12:22	.....	168	252	0.67 0.69	27 27	
12:55	.....	172	250	0.69	27	
3:00	.....	170	233	0.73	26	
3:26	.....	157	227	0.70 0.72	25 25	
3:54	.....	186	231	0.72	25	
4:45	.....	...	...	.....	.....	0.19

TABLE 23.—Effect of Oatmeal on the Respiratory Quotient of a Severe Diabetic

Case 773. Female. Weight 40 kilos.

Date	Condition	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.	Cals. per Kilo per 24 Hrs.	Blood Sugar Per Cent.
10/10/14 8:00	Fasting.....	146	212	0.69	30	
	Oatmeal = 42 gm. carb.					
11:00	.....	178	249	0.72	42	
10/13/14 8.00	Fasting.....	156	189	0.73	33	0.32
11:00	.....	...	...	.....	.....	0.27
10/19/14 9:00	Fasting.....	135	195	0.70	34	0.27
	Oatmeal = 80 gm. carb.					
12:00	.....	167	237	0.70	40	0.30
10/20/14	After breakfast....	...	...	.....	.....	0.34

Diet contained 15 gm. carb. October 9 and October 18.

TABLE 24.—Effect of Oatmeal on the Respiratory Quotient of Severe Diabetics

Case No.	Duration		Date	Carbohydrates Ignited		Respiratory Quotient		Sugar in Urine, Gm.	Carb. Intake, Gm.	Carb. Balance, Gm.
	Onset to Coma, Months	Month of Test		Day Preceding, Gm.	Before Test Gm.	Fasting	After Oatmeal			
194	34	31	9/22	15	...	0.74	....	42	15	−27
			9/23	15	100+	0.71	0.71	50	165	+115
			9/24	165	...	0.72*	....	19	15	−4
246	15	11	8/ 9	80	40	0.71	0.67	124	?	?
		13	10/29	65	60	0.68	0.70	100	125	+25
			10/30	125	...	0.71*	....	98	65	−28
			10/25-31	71	...	0.69	....	102	72	−30
281	19	17	12/ 1	15	...	0.75	....	60	135	+66
			12/ 2	135	29	....	0.70*	58	45	−13
			12/ 3	45	0	0.76	....	38	30	−8
322	28	12	5/19	100	25±	....	0.73	15 in 3 hrs.		
			5/26	95	...	0.73	....	3 in 3 hrs.		
		24	4/ 2	?	52	0.74	0.74	97		
		26	6/ 2	?	48	0.71	0.69	26		
336	132	127	5/18	20	...	0.73	....	26	45	+19
			5/21	45	25	....	0.75	31	45	+14
441	11	9	9/29	15	75	0.70	0.71	65	165	+100
		10	10/ 9	15	73	....	0.69	?	79	
561	33	23	2/ 7	60	...	0.75	....	31.1	60	+30
			2/ 8	60	116	0.71	0.74	128.4	185	+57
			2/ 9	185	200	0.72*	0.72*	209.3	205	−4
			2/10	200	...	0.76†	....	101.86	60	−42
591	50	44	4/10	?	...	0.74	....	63	30	−33
			4/11	30	...	0.73	....	37	15	−22
			4/12	15	80	0.70	0.70	85	165	+80
			4/13	165	80	0.73*	0.69*	77	165	+88
			4/15	40	...	0.69	....	29	?	
773	20	18	10/ 8	115	70	....	0.70	175.6	165	−10
			10/10	15	47	0.69	0.72	95.4	130	+35
			10/13	50	...	0.73	....	83.97	50	−34
			10/19	15	80	0.70	0.70	96.50	115	+18
746	22‡	18	10/ 7	65	28	....	0.73	93.11	65	−28
			10/ 9	15	50	0.73	0.71	86.69	163	+76
			10/10	165	...	0.72*	....	34.88	25	−10
			10/15	165	80	....	0.74†	96.28	165	+69
786	17‡	14	11/12	15	69	0.69	0.73	0	62	+62

* R. Q. taken following an oatmeal day.
† R. Q. taken subsequent to two oatmeal days.
‡ Prior to March, 1915.

oatmeal. It will be seen from a study of the tables that as a rule the respiratory quotient remained stationary or fell; in one case it rose 4 points, and in two other cases it rose one point. It will be noted further that the respiratory quotient, when taken fasting on the morning following an oatmeal day, amounted in three cases to 0.73, 0.72 and 0.73 respectively, and that on the morning following a second oatmeal day it was 0.69 and 0.76. The respiratory quotient was also determined in three experiments after the administration of carbohydrate and on the second day it was 0.72. If one looks at the table as a whole, it will be seen that little change in the respiratory quotient took place: in fact, none of any account except on the morning following the second oatmeal day.

The sum total of the results following the feeding of levulose, potato and oatmeal to severe diabetics affords little evidence, from the respiratory quotient, that the carbohydrate was burned, save in the case of one of the experiments with levulose, one with potato, and one with oatmeal. There results correspond closely with what has been recorded in the literature. Personally, I believe that before a final decision on this point can be reached from this particular line of study, further experiments must be performed.

Unfortunately in the experiments recorded no stated agreement was noted between changes in respiratory quotient and variations in the quantity of blood sugar. From Table 6 it is evident that there is a general tendency for the respiratory quotient to rise with an increase in blood sugar, but this may be accidental. Studies now in progress will soon throw light on this phase of the question.

V. ACIDOSIS AS A MEASURE OF THE UTILIZATION OF CARBOHYDRATES

It has been generally accepted that acidosis will appear when carbohydrate food is either withdrawn from the diet or excreted in the urine. It has been unquestionably the universal clinical experience that the patient who excretes quantities of sugar in the urine equal to or in excess of that in the diet exhibits acidosis, and that patients do not show acidosis who are able to utilize approximately 70 gm. of carbohydrate, or large quantities of protein from which carbohydrate may be formed. This statement cannot be so unqualifiedly made, because I have under observation a woman who in her sixth month of pregnancy showed over 6 per cent. of sugar, and later under a careful diet became sugar-free, acquired a tolerance for approximately 100 gm. of carbohydrate, and yet a slight acidosis persisted. Nevertheless, the general mass of evidence points to the disappearance of acidosis when carbohydrates are burned, and on this general concept arguments have been based for and against the utilization of carbohydrate in severe diabetes.

During von Noorden's oatmeal treatment a considerable quantity of carbohydrate ingested is usually retained or burned in the body, and the decrease of acidosis at the same time is usually considered evidence of the latter supposition being correct, but occasionally the acidosis persists although the carbohydrates are not excreted. I doubt if we are in a position to accurately explain the disappearance or non-disappearance of acidosis under these conditions. Oatmeal and other carbohydrates are better retained in the body following starvation, and it is quite possible that a mechanical retention of acid bodies goes hand in hand with the retention of carbohydrate. Magnus-Levy pointed out long ago that these were seldom excreted in concentration of more than 1.5 per cent., and that the fall in acidosis during an oatmeal cure may be simply apparent, because the volume of urine excreted has diminished. The influence of preceding fasting is also important, because this undoubtedly regulates to some extent the storage of carbohydrate. Despite these possibilities, which lessen any argument for combustion of carbohydrate based on the decrease of acidosis following the ingestion of carbohydrate, the slight amount of acidosis which is usually found when diabetic patients are on a full carbohydrate diet points strongly to the view that some carbohydrate is burned. The increase in respiratory quotient on the last days of an oatmeal cure, which Falta observed and we also have noted, is conformatory to this position.

Various writers have observed that the acidosis in diabetics decreases on a vegetable day or fasting day, but it remained for Allen to demonstrate conclusively the remarkable fact that acidosis vanished in practically all severe cases of diabetes under these conditions, and that in the remainder, if carbohydrates to a moderate extent are allowed temporarily the acidosis wholly clears up. If a normal individual fasts, it has been the universal experience of observers that acidosis appears. In other words, the normal fasting individual corresponds with the concept that when carbohydrates are withdrawn from the diet (and this implies carbohydrates which might be formed from protein) acidosis appears. Thus, in the fasting man at the Nutrition Laboratory, acidosis appeared on the second day and continued until the fast was terminated. How can we reconcile the apparent contradiction in the fact that fasting, which dissipates acidosis in diabetes, produces it in normal individuals? Must the prevalent conception be given up that carbohydrate oxidation and acidosis are unrelated and must we acknowledge that here is an instance where the absence of the burning of carbohydrates does not lead to acidosis? Such a conclusion appeared unavoidable until observations at the Nutrition Laboratory on severe diabetics during prolonged fasting began to accumu-

late, showing that whereas at the beginning of the fast the respiratory quotient was the ordinary respiratory quotient of severe diabetes, 0.72, with a continuance of the fast this had a tendency to rise several points, occasionally even to the neighborhood of 0.80. Later experiments, as yet unpublished, at the Russell Sage Laboratory made under the direction of Dr. DuBois and Professor Lusk on one of Dr. Allen's patients suggested a similar condition. In other words, whereas the normal individual showing acidosis exhibits a respiratory quotient based on the combustion of protein and fat alone, the severely affected diabetic during fasting shows a respiratory quotient which could be accounted for only by the combustion of notable quantities of material other than fat and protein. That this material was not protein was evident, because the amounts of nitrogen in the urine excreted during these periods were not abnormal. This increase in the respiratory quotient furnishes the explanation of the fact that the severely affected diabetic in contradistinction to the normal individual, shows no acidosis during a fast.

Several explanations for this increase in the respiratory quotient of fasting diabetics are available. During fasting the diabetic may be able to draw on sources of carbohydrate in the body which the normal individual cannot. Furthermore, the diabetic has in the body undoubtedly more carbohydrate stored than we have hitherto supposed, and the supposition must be entertained that the diabetic really may actually have more carbohydrate in some form in the body than exists in the normal individual. A third supposition for the increase in the respiratory quotient is that considerable quantities of acid bodies have accumulated and that with the improvement of the condition of the patient during fasting these are burned. It will be remembered that beta-oxybutyric acid, diacetic acid and acetone all have relatively high respiratory quotients, namely, 0.89, 1.00 and 0.75 respectively, and therefore the oxidation of a small quantity of these substances would markedly raise the respiratory quotient. Which of these suppositions is correct will be eventually known because of the improved methods of estimating carbohydrate and acid bodies in the blood, fluids and tissues of the body,[39] and also by the help which is afforded from the estimation of the carbon dioxid tension of the blood.

I should like to point out this further possibility: During prolonged fasting, acidosis tends to disappear, in part because the sources of the acid bodies, save for body fat and protein, have been eliminated. So soon as acidosis begins to decrease, there is, as we and others have found, a lessening of the total metabolism, and with this lessening of total metabolism an improvement in the combustion of carbohydrate

39. Marriott: Jour. Am. Med. Assn., 1914, lxiii, 397.

takes place. This in turn favors the combustion of acid bodies. It might well be that the first step to take in the treatment of a case of diabetes is to abolish acidosis completely.

All may be ready to concede that all diabetic patients under fasting conditions are burning carbohydrates, but some may say that the character of the disease has changed, and instead of being a severe type of diabetes the case has become one of moderate severity. Such a criticism is hard to answer. It presupposes, however, that an individual can readily change in the space of a few hours from a state in which death is imminent to one of safety, and that so fundamental a function as the loss of power to utilize carbohydrates can be quickly regained. This would be a remarkable phenomenon. Against this explanation also is the fact that many who have employed fasting treatment with severe cases of diabetes have regretfully acknowledged that either very slight or no increase of tolerance for carbohydrates has been produced in these patients. This would make it still more unlikely that the diabetic patient by fasting altered his nature. It would rather point to the view that the diabetic condition remained unchanged, but that during fasting the diabetic was able to secure and burn material which under other conditions he could not reach, and which the normal individual could not secure.

In conclusion it is gratifying to be able to record that the recent experimental evidence confirms the old clinical view that the severe diabetic still retains power to utilize a portion of the carbohydrate of his diet, small though it may be and that herein lies renewed hope for the success of treatment.

81 Bay State Road.

RENAL FUNCTION AS MEASURED BY THE ELIMINATION OF FLUIDS, SALT AND NITROGEN, AND THE SPECIFIC GRAVITY OF THE URINE*

HERMAN O. MOSENTHAL, M.D.
BALTIMORE

During the last few years the study of renal function has largely confined itself to the determination of kidney activity as measured by the quantitative excretion of various dyestuffs and chemicals, either those normally found in the urine or foreign substances which have been fed or injected. By observing the kidney in this manner, notable results have been obtained, especially with phenolsulphonephthalein, lactose, potassium iodid, urea, salt and kreatinin. In most instances, the outcome of intensive study has been the discovery that the elimination of nearly all of these substances may at times be increased quantitatively, in spite of marked renal lesions, or their complications, such as uremia. To supplement such tests, Hedinger and Schlayer[1] have recently proposed a qualitative test of the mode of urinary function, as measured by the specific gravity, salt and water excretion in two-hourly periods. These authors show how the urinary response to a full dietary containing a reasonable amount of fluids, salt and purins varies in health and disease. They found that the normal and the nephritic individual differ very markedly from one another in the results obtained with the so-called "nephritic test meal." Not only can the absence or presence of impairment of renal function be determined, but likewise its intensity.

The present paper records the results of studies carried out along lines suggested by this work. The test meal has been simplified somewhat, and it appears that the entire procedure, or a part of it, may very well become a valuable routine test for the general practitioner.

This test has now been carried out in more than one hundred cases. The only patients not investigated, in whom renal function should be ascertained, were those suffering from the acute nephritides; of these, such as have been treated in the wards of the hospital during the past winter have been too sick to take food in any qantity, or have been so unmanageable as to preclude the proper collection of specimens. It has been ascertained that the nephritic test meal, when duplicated on

* Submitted for publication July 29, 1915.
* From the Medical Clinic of the Johns Hopkins Hospital, Baltimore.
1. Hedinger and Schlayer: Deutsch. Arch. f. klin. med., 1914, cxiv, 120.

the same patient, yields identical results, provided the clinical condition has not changed. In several instances triplicate and quadruplicate observations have been made. Lack of space prevents the detailed report of all the findings.

The directions for the nephritic test meal are contained in the following memoranda, given to the nurse in charge of the case in mimeographed form:

NEPHRITIC TEST DIET

For ..... Date .....

All food is to be *salt free* food from the diet kitchen.

Salt for each meal will be furnished in weighed amounts.*

All food or fluid not taken must be weighed or measured after meals and charted in the spaces below.

Allow no food or fluid of any kind except at meal times.

Note any mishaps or irregularities that occur in giving the diet or collecting the specimens.

Breakfast, 8 a. m.

Boiled oatmeal, 100 gm.....
Sugar, 1-2 teaspoonfuls.....
Milk, 30 c.c.....
Two slices bread (30 gm. each).....
Butter, 20 gm.....
Coffee, 160 c.c. } 200 c.c.....
Sugar, 1 teaspoonful } .....
Milk, 40 c.c. } .....
Milk, 200 c.c.....
Water, 200 c.c.....

Dinner, 12 Noon.

Meat soup, 180 c.c.....
Beefsteak, 100 gm.....
Potato (baked, mashed or boiled), 130 gm.....
Green vegetables, as desired.....
Two slices bread (30 gm. each).....
Butter, 20 gm.....
Tea, 180 c.c. } 200 c.c.....
Sugar, 1 teaspoonful } .....
Milk, 20 c.c. } .....
Water, 250 c.c.....
Pudding (tapioca or rice), 110 gm.....

Supper, 5 p. m.

Two eggs, cooked in any style.....
Two slices bread (30 gm. each).....
Butter, 20 gm.....
Tea, 180 c.c. } 200 c.c.....
Sugar, 1 teaspoonful } .....
Milk, 20 c.c. } .....
Fruit (stewed or fresh), 1 portion.....
Water, 300 c.c.....

8 a. m.—No food or fluid is to be given during the night or until 8 o'clock the next morning (after voiding), when the regular diet is resumed.

Patient is to empty bladder at 8 a. m. and at the end of each period, as indicated below. The specimens are to be collected for the following periods in properly labeled bottles, to be furnished by the Chemical Division of the Medical Clinic:

---

* One capsule of salt, containing 2.3 gm. of sodium chlorid, is furnished for each meal. The salt which is not consumed is returned to the laboratory, where it is weighed, and the actual amount of salt taken is calculated.

8 a. m.-10 a. m.; 10 a. m.-12 n.; 12 n.-2 p. m.; 2 p. m.-4 p. m.; 4 p. m.-6 p. m.; 6 p. m.-8 p. m.; 8 p. m.-8 a. m.

Specimens are to be left in ward until called for at 8:30 a. m. by attendant from the chemical laboratory.

The above dietary contains approximately 13.4 gm. of nitrogen, 8.5 gm. of salt, 1,760 c.c. of fluid, and a considerable quantity of purin material in the meat, soup, tea and coffee. All these substances act as diuretics, and it is on the mode of excretory response to such stimuli that the present study of renal function depends. Spaces are provided to chart the amounts of food not eaten by the patient, and corresponding allowances can be made in calculating the food intake. It is in no way essential that all the meals should be taken in their entirety, nor that the food should be exactly as indicated. The bill of fare here presented has been designed to adapt itself to the daily food supply furnished by the hospital. In private practice, it would only be necessary to ask the patient to eat three full meals a day and write down the approximate quantities, as—1 cup of coffee, 2 slices of toast, 2 tablespoonfuls of oatmeal, etc., in order to be certain that the diet for the day contained a sufficient quantity of the diuretic materials of our ordinary food to make an adequate demand on the kidney to test renal function. It is extremely desirable to insist on the fact that, since the food as found in most households suffices to carry out these tests and the procedure is not a complicated one, it need not be confined to hospitals and patients who can afford private nurses.

A wide variation may be permitted in the above-mentioned directions. Certain others, however, must be followed slavishly, in order to make the outcome of the test yield its maximum result. The urine must be collected punctually every two hours. No solid food or fluid of any kind must be taken between meals, and especial care must be observed that nothing of any kind is eaten or drunk during the night, and that the night specimen is completed before breakfast is touched. The reason for this is that the normal kidney responds rapidly to fluids ingested, so that within a few hours a marked diuresis occurs. The following observation may serve as an illustration of this previously well-established fact:

Time Interval	Urine Volume, c.c.	Fluid Ingested
6 p. m.- 8 p. m.	84	7:30 p.m. supper with
8 p. m.-10 p. m.	590	1,000 c.c. of water.
10 p. m.- 8 a. m.	361	

In this instance, within two and one-half hours of drinking 1,000 c.c. of water, over 590 c.c. were eliminated, while during the eight-hour period following the diuresis, only 361 c.c. of urine were voided.

The volume in cubic centimeters and the specific gravity of each specimen collected are determined. At the outset of the investigation,

the salt and nitrogen[2] were measured in each specimen. It soon became apparent, however, that it was necessary to make these calculations only in the total day and night urines. The normal curves show agreement with one another in many respects, and are apparently divergent in others. A considerable number of tests were made on other normal individuals, but yielded nothing further than is known here. The important points to be noted are the following:

1. The characteristics of the day urine.
2. The quantity of water, salt and nitrogen excreted in twenty-four hours.
3. The characteristics of the night urine.

These will be taken up in detail. The phenomena to be observed by means of the test meal may be obtained from specimens passed from day to day, and in patients who are involuntary or irrational, such piecemeal studies may become necessary. Although these have the disadvantage of being long drawn out and usually incomplete, it is surprising how many valuable data may be gleaned in this way, if the points to be noted are kept in mind.

THE NORMAL URINARY RESPONSE TO THE NEPHRITIC TEST MEAL

This is seen in Charts 1, 2, and 3 and Tables 1, 2, and 3. These three examples differ from one another in that the first subject is putting out an approximately normal quantity of fluid in relation to the amount of solids excreted; the second an abnormally large volume of urine (this individual, as a rule, took no tea or coffee and very little meat; the unaccustomed dose of purins of the test meal dietary, therefore, probably produced this great diuresis); the third, a subnormal quantity (a diminished amount of fluids being taken to note this effect). It should be borne in mind that the response to the nephritic test meal in normal individuals is practically always as in Charts 1 or 2. The type in Chart 3 may serve as a control for those pathological cases in which only a small amount of fluid is excreted. The facts to be noted are as follows:

In order to make the results of the test comprehensible at a glance, a graphic representation of the findings has been adopted, as shown in the accompanying charts (Charts 1 to 20 inclusive).

Explanation of the Charts.—Each chart is divided by two horizontal lines into three tiers. The lowest of these gives the figures for water and specific

2. The salt was estimated by the Volhardt method, nitrogen by the Kjeldahl process. Where more extensive laboratory facilities are not at hand, the method of Strauss, as advocated by Bayne-Jones (THE ARCHIVES INT. MED., 1913, xii, 90) for chlorids, and the hypobromid determination for urea will yield results that are easily obtained and are perfectly adequate from a practical point of view.

gravity, the middle for nitrogen and the upper for sodium chlorid. Each is further divided by a central vertical line into right and left halves. The left half, with its scale at the extreme left, contains six columns for the two-hourly specimens collected between 8 a. m. and 8 p. m. Each column represents absolute values. The right half is read by the scale at the extreme right, whose divisions are usually equivalent to one-tenth of those on the left, but rarely, as in Chart 2, to one-fifth, to bring unusual figures within the compass of the chart. The columns of this right half are two pairs, separated by a space. The central pair represents the total night and the total day twelve-hour figures for volume, nitrogen and sodium chlorid, night in solid black and day in oblique hatching at its right. The pair at the extreme right represent intake and output for the whole twenty-four hours, intake at the left in vertical, output at the right in cross or oblique hatching The dots joined by continuous lines crossing each tier from left to right indicate the specific gravity and the percentage concentrations of nitrogen and sodium chlorid, respectively, and are read from the scale at the left.

TABLE 1.—NORMAL REACTION TO NEPHRITIC TEST MEAL

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	153	1.016	1.32	2.02	0.89	1.26
10-12	156	1.019	1.25	1.95	0.74	1.15
12- 2	194	1.012	0.64	1.24	0.59	1.14
2- 4	260	1.014	0.77	2.00	0.56	1.46
4- 6	114	1.020	0.99	1.13	0.95	1.08
6- 8	238	1.010	0.43	1.02	0.52	1.23
Total day	1,115	.....	....	9.36	....	7.32
Night, 8-8	375	1.020	0.63	2.36	1.23	4.61
Total 24 hours	1,490	.....	....	11.72	....	11.93
Intake	1,760	.....	....	8.5	....	13.4
Balance	+270	.....	....	—3.22	....	+1.47

Impression (the figures correspond with Chart 1): Normal reaction to the nephritic test meal. Note the variations occurring in the fluid output, and the specific gravity, which are in inverse ratio; the night urine, which is small in amount and shows a high specific gravity and a high percentage of nitrogen; and the approximately normal output of water, salt and nitrogen in twenty-four-hours.

TABLE 2.—NORMAL REACTION TO NEPHRITIC TEST MEAL

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	240	1.018				
10-12	482	1.010				
12- 2	244	1.019				
2- 4	290	1.010				
4- 6	120	1.017				
6- 8	420	1.007				
Total day	1,796	.....	0.66	11.84	0.41	7.36
Night, 10-8 ...	352	1.017	0.58	2.16	1.20	4.22
Total 24 hours	2,148	.....	....	14.00	....	11.58
Intake	1,760	.....	....	8.50	....	13.40
Balance	—388	.....	....	—5.50	....	+1.82

Impression (the figures correspond with Chart 2): Normal reaction to the nephritic test meal. In this case, polyuria is evident. This is probably due to the reaction in an individual who is accustomed to a bland diet and not to the quantities of salt and purins taken with the test meal.

TABLE 3.—Normal Reaction to Nephritic Test Meal

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid		Nitrogen	
			Per Cent.	gm.	Per Cent.	gm.
8-10	90	1.026	1.23	1.11	1.39	1.25
10-12	78	1.027	1.29	1.01	1.58	1.24
12- 2	114	1.027	1.27	1.45	1.30	1.48
2- 4	75	1.030	0.97	0.73	1.77	1.33
4- 6	85	1.030	1.20	1.01	1.66	1.42
6- 8	104	1.028	1.06	1.10	1.52	1.58
8-10	88	1.024	0.83	0.73	1.37	1.20
Total day	634	.....	....	7.14	....	9.50
Night, 10-8 ...	290	1.027	0.73	2.12	2.07	6.00
Total 24 hours	924	.....	....	9.26	....	15.50
Intake	1,100	.....	....	9.00	....	16.00
Balance .....+	176	.....	....	—0.26	....	+ 0.50

Impression (the figures correspond to Chart 3): Normal reaction to the nephritic test meal. In this test the fluid was limited and the solid food increased, so as to produce a concentrated urine, as occurs in myocardial decompensation. The characteristics of the normal response, rise of urine volume after each meal, the variation of specific gravity, the small volume of night urine with a high concentration of nitrogen and high specific gravity, and an approximate balance of fluid, salt and nitrogen, are all present in spite of the restrictions imposed. (In this case supper was taken at 7 p. m. The collections of night urine were, therefore, begun at 10 p. m. instead of at 8 p. m.)

1. *The Day Urine.*—This shows a rhythmical response to each meal in that the quantity of fluid increases at these periods. This is well shown in Chart 3; in Charts 1 and 2 certain irregularities in the diuresis following food ingestion are seen. In Chart 1 there is no distinct polyuria after breakfast and that after the mid-day meal occurs late. A similar delayed polyuria is found on Chart 2. The diuretic response to each meal in the two-hourly periods was not as constantly present as Hedinger and Schlayer found it to be. In fact, at times it is almost entirely suppressed, as is seen in the following instance, in which the rise of urine after supper is distinct, the other responses being masked or absent:

Time of day.....	*8.10	10-12	*12-2	2-4	4*6	6-8
Volume of urine, c.c.....	118	146	157	180	170	261

* Indicates the meal hours.

Because of the irregularity of this symptom in normal cases, not very much stress has been laid on its absence in interpreting pathological urines. However, a fixed or constant two-hourly output has proved itself to be of considerable significance in interpreting renal function in some patients.

The specific gravity of the two-hourly specimens is not fixed, but varies inversely to the volume of urine; this is not as markedly the case in Chart 3, where the induced oliguria requires a urine of moderately constant high specific gravity in order to eliminate the required quan-

tity of solids. However, even in this case, the variations in specific gravity are by no means confined within one or two points, as they are in many of the pathological specimens. Table 4 gives a summary of these observations:

TABLE 4.—SUMMARY OF SPECIFIC GRAVITY OBSERVATIONS IN NORMAL INDIVIDUALS

Case	Maximum	Minimum	Difference
1	1.020	1.010	10
2	1.019	1.007	12
3	1.031	1.024	7
4	1.019	1.009	10
5	1.020	1.007	13
6	1.025	1.005	20
7	1.023	1.010	13
8	1.018	1.008	10
9	1.018	1.007	11
10	1.019	1.007	12
11	1.026	1.014	12
12	1.030	1.010	20

The maximum and minimum figures for urinary specific gravity, as found in the specimens collected in two-hour periods during the day from normal individuals on a nephritic test diet. Note the marked variation between the highest and lowest observations in each instance. The lowest variation occurs in Case 3 (see Table 3); this is due to the fact that in this individual water intake was much restricted.

2. *The Quantity of Water, Salt and Nitrogen Excreted in Twenty-Four Hours.*—Normally the urinary fluid output should be about 400 c.c. less than the intake, to allow for the excretion of water by the lungs, skin and intestines. About 90 per cent. of the nitrogen ingested should be found in the urine, the remainder passing out in the feces. The sodium chlorid as found in the urine represents practically the total excretion of this substance except in cases of diarrhea. These statements hold true for carefully regulated metabolism studies carried on over several days, but it must be remembered that the previous habits have a very great bearing on tests such as those under consideration here. Thus it has been noted, on comparing Charts 1 and 2, how a full diet produces polyuria in an individual who has been accustomed to very bland food, and furthermore, it is found that a comparatively small amount of urine is produced by an individual who on the previous day has drunk too little fluid to meet his requirements. Various and often easily ascertainable reasons may exist for either retention or an excess of excretion, which may lead us to look on these phenomena as presenting no abnormalities. However, they should always be regarded with suspicion and be thoroughly considered in their bearing on the case in question. Vastly more important is the concentration of salt and nitrogen in the urine. A normal kidney can readily concentrate nitrogen and salt above 1 per cent.; an abnormal kidney often

can not. Therefore, the total quantity of urine and urinary ingredients excreted is to be observed, but particular stress is to be laid on the concentration of nitrogen and salt.

3. *The Characteristics of the Night Urine.*—Whatever the quantity of urine excreted during the day, it is found that the night specimen varies within very narrow limits. The precautions of not allowing water at night time, previously dwelt on, must be strictly carried out to make this observation of value. In the night urine, as a rule, the concentration of nitrogen and the specific gravity are high. The figures for normals, as given in Table 5, substantiate these statements.

TABLE 5.—Comparison of Night and Day Urines in Normal Individuals

	——Night Urine (12 Hours)——			Day Urine
Case	Specific Gravity	Nitrogen Per Cent.	Volume c.c.	(12 Hours) Volume, c.c.
1	1.020	1.23	375	1,105
2	1.017	1.20	352	1,796
3	1.027	2.07	290	634
4	1.019	1.12	350	1,032
5	1.018	1.03	390	1,945
6	1.018	1.43	361	1,413
7	1.019	1.14	355	2,156
8	1.018	1.08	402	2,446
9	1.026	1.42	277	866
10	1.030	1.58	210	1,496
11	1.029	1.85	213	468
12	1.025	1.23	248	861

The nitrogen percentage, specific gravity and volume for the night urines of normal individuals on a nephritic test diet. Note the high percentage of nitrogen, high specific gravity and the small volume of urine, as compared to the day specimen.

The most important points to be observed in the urine of normal individuals on the nephritic test meal are:

1. Variations in the specific gravity of the urine specimens (usually 10 points or more; in cases of diminished water intake and oliguria, the variations may be somewhat less).

2. The balance between the output and intake of salt, nitrogen and fluids. This should be approximately equal.

3. A night urine high in specific gravity (1.016, but usually 1.018 or higher), high in its percentage of nitrogen (above 1 per cent.) and small in amount (400 c.c. or less), regardless of the quantity of fluid ingested or the amount of urine voided during the day.

THE URINARY RESPONSE TO THE TEST MEAL IN DISEASE

The individual factors will be first discussed and then applied to special cases.

1. *The Day Urine.*—Koranyi[3] summarized the essential findings of his own and others' work in relation to these problems. These are in full accord with the facts as substantiated by Hedinger and Schlayer[1] and in the present observations. The kidney expresses its diminished power to functionate by a fixation of its concentration. The normal kidney yields a urine of medium, low or high specific gravity (Table 4) according to the proportion of fluids and solids that must be excreted in order to maintain the composition of the body fluids at a constant level. The diseased kidney, on the other hand, loses this flexibility and the power to answer a demand for a more concentrated or more dilute urine no longer exists. This condition Koranyi has spoken of as hyposthenuria. Koranyi emphasizes the fact, which is usually not sufficiently appreciated, that the power to excrete a more dilute urine is lost, as well as that to concentrate (Chart 6). Such a fixation of specific gravity appears when the kidney is the seat of a nephritis, but the fact must not be lost sight of that extrarenal factors may damage kidney function to an equal extent. This fixation of specific gravity occurs in nephritis, pyelitis, cystitis associated with prostatic

TABLE 6.—SPECIFIC GRAVITY OF URINES COLLECTED IN TWO-HOURLY PERIODS

Case	Specific Gravity*						Degrees of Variation in Readings
Normal (Chart 1)	16	19	12	14	20	10	10
Incipient primary contracted kidney	09	14	09	10	14	06	8
Incipient primary contracted kidney	18	09	16	22	13	10	11
Advancing primary contracted kidney	18	17	13	13	13	15	5
Advancing primary contracted kidney	19	20	20	20	21	20	2
Advanced primary contracted kidney	11	11	10	11	11	11	1
Advanced primary contracted kidney	12	11	11	11	12	13	2
Advanced primary contracted kidney	10	09	10	09	09	10	1
Advanced primary contracted kidney	05	06	07	08	..	08	3
Incipient chronic diffuse nephritis	25	..	24	33	28	30	9
Incipient chronic diffuse nephritis	09	16	15	17	12	07	10
Advanced chronic diffuse nephritis	12	11	14	11	13	11	3
Secondary contracted kidney	09	10	12	10	12	10	3
Congested kidney; myocardial decompensation marked	18	20	19	18	20	21	3
Congested kidney; moderate myocardial decompensation	25	24	24	25	24	21	4
Congested kidney; cardiac compensation; losing edema	12	15	10	15	13	10	5
Congested kidney; cardiac compensation; edema disappeared	05	06	11	09	09	10	5
Polycystic kidney	10	10	10	11	10	10	1
Marked anemia	10	10	10	10	10	11	1
Diabetes insipidus	04	04	06	04	04	04	2
Cystitis, pyelitis, prostatic hypertrophy	10	10	10	10	11	11	1
Pyonephrosis	11	12	12	13	12	12	2

* Variations of specific gravity in the day urine collected in two-hourly intervals. Note the fixed specific gravity of the severe cases of nephritis. Only the last two figures of each reading are given.

3. Koranyi and Richter: "Physiakalische Chemie und Medizin," Leipzig, 1908, ii, 136-152.

hypertrophy, hydronephrosis, pyonephrosis, polycystic kidneys, renal congestion due to cardiac disease, both in the stage of decompensation and in the early stages of recovering compensation, diabetes insipidus, severe anemias, and possibly in other conditions.

Table 6 shows the specific gravities of some of these urines, as found in the two-hourly diurnal periods.

The figures in Table 6 bear out what has been said, and demonstrate how extreme a fixation of urinary concentration may become. In this connection the data given in Table 7 are also of interest, showing how a low specific gravity may remain a fixture from day to day in nephritis, in the diurnal as well as the nocturnal specimens:

E. F. (Medical No. 33757), male, aged 36. Albumin was discovered in the urine seventeen years ago. For five years there has been polyuria and polydipsia; for two years, failing vision. There is moderate thickening of all the peripheral arteries. The cardiac impulse is forcible in the fifth interspace, 12.5 cm. to the left of the median line, indicating some hypertrophy of the heart muscle. There is no edema, nor are there other signs of myocardial insufficiency. The systolic blood pressure varies between 210 and 195 mm. of mercury. The eyegrounds show marked albuminuric retinitis. The urine is large in amount, constantly low in specific gravity, contains about 1 gm. of albumin per liter, and on microscopic examination yields a few hyaline casts. The phenolsulphonephthalein excretion is 22 per cent. in two hours. The nonprotein nitrogen of the blood is 59 mg. per 100 c.c. The diagnosis is an advanced degree of chronic diffuse nephritis (secondary contracted kidney).

The night and day urines followed over a considerable period gave the figures shown in Table 7.

TABLE 7.—Showing the Constancy of Nocturnal Polyuria and Low Specific Gravity in the Urine of a Case of Advanced Chronic Diffuse Nephritis

Volume of Urine, c.c.		Urinary Specific Gravity *	
Day	Night	Day	Night
1,390	560	12	10
935	710	12	11
1,010	760	11	10
1,122	705	10	10
790	790	10	10
908	1,110	11	10
880	1,184	11	10
1,020	1,360	12	09
1,075	1,120	11	10
1,140	1,255	10	10
1,375	730	12	11
1,600	1,160	12	10
1,525	1,090	12	11
1,400	1,260	11	10
1,146	1,100	11	12
1,940	1,060	10	09
1,280	1,520	10	09
1,640	1,400	10	10
1,370	1,370	11	10
1,480	1,480	18	18
1,340	1,680	19	17
1,410	1,340	10	10
1,480	1,410	12	10
1,185	1,610	10	08

* Only two last figures are given.

On two days (towards the lower portion of the table) the specific gravity rose to about 1.018. This is the only case of advanced nephritis with a tendency to low specific gravity in which a variation of this kind was noted. In chronic diffuse nephritis, such changes in the level of concentration are common, but they occur gradually, being associated with definite phases of the disease. (Compare Charts 17 and 18.) Von Noorden[4] contends that all cases of contracted kidney pass a low specific gravity urine because of polydipsia, that they all concentrate the urine in some specimen during a part of the day, and that it is wrong to assume an obligatory hyposthenuria on their part. The figures of Table 6 indicate no variability in the day urine of these cases and all attempts to limit the water of such individuals have been found to be impracticable. The impression gained from these studies is that pathologic lesions of the kidney are responsible for the low fixed specific gravity of the urine and that, with rare exceptions, when once established it remains constantly low.

The level of the fixed specific gravity changes under certain conditions. Besides the cases of chronic diffuse nephritis just referred to, this is noted in myocardial insufficiency, in which it is constantly high (Charts 13 and 14), until compensation is established, when it assumes a lower level (Chart 15). Even then, when all edema has disappeared and it would be expected that the renal functions had returned to normal, this anomaly of urinary secretion, a low moderately fixed specific gravity, persists (Chart 16). It accentuates the fact that functional and anatomical integrity are not synonymous terms.

The water excretion is very often found to remain markedly constant in quantity in the two-hourly periods, as does the level of the specific gravity (Charts 6, 10, 11 and 12). This factor may be of value in estimating renal function; however, it was found to be of much less significance than the specific gravity in the tests here reported, and consequently the greatest stress has been put on the latter. The salt and nitrogen percentages of the urine exhibited the same tendency to a constancy in their percentage values as did the specific gravity figures. (Compare Charts 1, 2, and 3 of the normal individuals with Charts 7 and 11). Here, again, nothing was added to the information gained from the specific gravity, and consequently, in order to simplify the whole procedure to its utmost, these determinations were omitted for the two-hourly specimens and ascertained only for the total day and night urines.

2. *The Quantity of Water, Salt and Nitrogen Eliminated in Twenty-Four Hours.*—Impaired renal function may be associated with

4. Von Noorden: Handbuch der Pathologie des Staffwechsels. Berlin, 1906, i, 994.

a retention of one or all of these elements. The cardiac and renal cases have been rather fully investigated in this connection and, as a result, certain definite conclusions may be formulated in regard to them.

When there is passive congestion of the kidney due to myocardial insufficiency, the amounts of water and sodium chlorid eliminated are much diminished, while the nitrogen excretion remains approximately normal. An extreme case of this kind was found in L. (Medical No. 33177), who, on autopsy, proved to have cardiac decompensation, brought on by a severe grade of myocarditis, thromboses of the coronary arteries and infarcts in the myocardium; the kidneys showed congestion only; urinary tests in this patient yielded the results shown in Table 8.

TABLE 8.—Results of Urinary Tests in Patient L. (Marked Myocardial Insufficiency)

Day	Urine Volume, c.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	gm.	Per Cent.	gm.
1	850	1.022	0.02	0.17	1.76	14.9
2	770	1.022	0.04	0.31	1.74	13.4
3	545	1.025	0.03	0.16	1.56	8.5
4	420	1.025	0.02	0.08	1.56	6.6

In such instances, the minimal concentration of salt and the high percentage of nitrogen indicate the very limited ability of the kidney to eliminate sodium chlorid, while the power to excrete nitrogen remains normal, provided a reasonable amount of urine is secreted.

Milder grades of myocardial decompensation yield similar results, though the sodium chlorid elimination is not diminished to the same extent. This is well shown in Charts 13 and 14. These and two similar cases may be summarized in Table 9.

TABLE 9.—Summary of Urine Tests in Cases of Myocardial Decompensation

Case	Urine Volume, c.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	gm.	Per Cent.	gm.
1	540	1.020	0.25	1.34	1.44	7.78
2	573	1.019	0.28	1.62	1.76	10.08
3	484	1.022	0.52	2.53	1.58	7.64
4	446	1.018	0.61	2.72	1.38	6.15

The low percentage of salt and the oliguria, as compared to the high concentration of nitrogen, are very strikingly shown in Table 9.

With recovery of cardiac compensation, the excretion of salt and water is much improved, as is seen in Charts 15 and 16. Many of these individuals, however, do not excrete the salt of their dietary completely. Retaining a small amount of salt on each day, they finally develop a marked edema. Under these circumstances, the curious picture often presents itself of a patient with general subcutaneous

edema, and possibly a transudate in one or the other of the body cavities, without dyspnea, marked cyanosis, or other signs of myocardial insufficiency. On the removal of salt from the food, the edema again disappears rapidly. Not all cases exhibit this inability to excrete sodium chlorid. Except by trial, there seems to be no way of distinguishing those that will from those that will not tolerate salt. It is a very important point, from the therapeutic side, and as much stress should be laid on the restriction of salt in these cases as on the limitation of fluids.

In nephritis, two distinct types of excretion are found:

1. Salt retention not associated with deficient nitrogen elimination. This is seen in the cases of chronic diffuse (parenchymatous) nephritis. The entire picture has had Widal's name associated with it for a long time. A test meal in a patient of this type yields the results shown in Table 10.

TABLE 10.—NEPHRITIC TEST MEAL IN A CASE OF CHRONIC DIFFUSE (PARENCHYMATOUS) NEPHRITIS

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	32	1.025				
10-12	0	.....				
12- 2	54	1.024				
2- 4	64	1.033				
4- 6	64	1.028				
6- 8	66	1.030				
Total day	280	.....	0.18	0.50	1.91	5.34
Night, 8-8	595	1.016	0.08	0.48	0.93	5.53
Total 24 hours	875	.....	....	0.98	....	10.87
Intake	1,760	.....	....	8.50	....	13.40
Balance	+885	.....	....	+7.52	....	+2.53

Impression: There is marked salt and water retention; the excretion of nitrogen is adequate. The variations in specific gravity distinguish this case from one of cardiac insufficiency, and indicate that renal function as a whole is not seriously impaired.

With rest and adequate treatment, the power to excrete salt and water is rapidly acquired, and the whole process of renal activity changes. A test meal in the same individual yields an entirely different set of figures under such circumstances (Table 11).

2. In advanced cases of primary or secondary contracted kidney, characterized by hypertension and termination in uremia, the quantities of salt and nitrogen excreted are both diminished. In none of these patients has much improvement in this regard been noted. In observing the urine of hypertensive nephritis, and attempting to couple it with constant clear-cut characteristics, the precaution must be taken to separate the uncomplicated cases from those associated with other

lesions, such as marked anemia, cardiac insufficiency, or bronchopneumonia. The analyses of the test meals in these individuals, all of them in advanced stages of the disease, are shown in Table 12.

TABLE 11.—NEPHRITIC TEST MEAL IN THE SAME CASE AS TABLE 10—SOME TIME LATER

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid		Nitrogen	
			Per Cent.	gm.	Per Cent.	gm.
8-10	137	1.015	0.82	1.12	0.70	0.95
10-12	148	1.016	0.82	1.11	0.80	1.18
12- 2	108	1.016	0.78	0.84	0.79	0.85
2- 4	184	1.015	0.57	1.04	0.79	1.46
4- 6	96	1.015	0.48	0.46	0.79	0.76
6- 8	470	1.004	0.30	1.45	0.25	1.18
Total day	1,143	.....	....	6.02	....	6.38
Night, 8-8	960	1.010	0.34	3.26	0.38	3.65
Total 24 hours	2,103	.....	....	9.28	....	10.03
Intake	1,760	.....	....	8.50	....	13.40
Balance	—343	.....	....	—0.78	....	+3.37

Impression: Water and salt are excreted in excess in contrast to previous meal. The polyuria, both during the day and night, and the rather low fixed specific gravity, are due to the fact that this patient is eliminating edema, and must not be confounded with similar curves obtained in case of hypertensive nephritis, where they would indicate a considerable degree of impaired renal function. On physical examination, the two conditions can very easily be distinguished from one another.

TABLE 12.—NITROGEN, SALT AND WATER EXCRETION IN ADVANCED UNCOMPLICATED INTERSTITIAL NEPHRITIS *

Case	Urine Volume, c.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	gm.	Per Cent.	gm.
1	776	1.014	0.37	2.88	0.65	5.08
2	1,282	1.013	0.29	3.69	0.52	6.71
3	1,276	1.012	0.42	5.41	0.49	6.28
4	1,535	1.009	0.35	5.34	0.42	6.51
5	1,873	1.011	0.41	7.64	0.14	2.59
5	1,541	1.010	0.30	4.70	0.30	4.64
7	1,665	1.009	0.12	2.00	0.09	1.50

* The approximate intake was 1,760 c.c. of fluid, 8.5 gm. of salt and 13.4 gm. of nitrogen in each case.

From Table 12 it is clear that the low specific gravity usually attributed to these cases has been found here as well, and that the urinary concentration of salt and nitrogen is so much depressed that there is retention of these substances.

When cases of this kind are complicated by various intercurrent factors, the same degree of impairment in the elimination of salt and water is not found even just before death. Fatal termination in them is hastened by anemia, heart failure, bronchopneumonia, etc., and hence the involvement of renal function does not have an opportunity to develop to its full extent. It may be that the lack of a uniform

picture in the urine of uremic patients (and even renal cases less severely affected) may be due to the tendency to place every case of hypertension in this category, regardless of whether any complications be present or not.

In no instance has the combination of nitrogen retention with sufficient salt excretion been met with.

3. *The Night Urine.*—Since the systematic and thorough observations of Quincke,[5] it has been recognized that a nocturnal polyuria is a valuable sign of impaired renal function. Through these, and the studies of v. Leube,[6] Runeberg,[7] Wilson,[8] Iljisch,[9] Laspeyres[10] and Pehu,[11] it has been shown that a supernormal quantity of urine at night, or nycturia, as it has been termed by Pehu, is significant of a variety of conditions. Acute or chronic nephritis, amyloid kidney, myocardial insufficiency, diabetes mellitus, cystitis, prostatic hypertrophy, and the excretion of edema, have all been found at times to produce a nycturia.

It is often noted in patients' histories that urine is voided two, three or more times during the night, and yet closer investigation shows this to be a nocturnal pollakiuria, not accompanied by an increase above the normal amount (400 c.c.). In some cases, a urethritis, prostatic hypertrophy or other local source of irritation may be found; in others, constituting a large number, the increased frequency of voiding at night can only be attributed to a nervous habit. Among many investigated with this point in view, the following may serve as an example: The patient complained of voiding four to ten times a night before admission; since entering the hospital he has passed his urine three or more times. In two twenty-four-hour periods the day urine amounted to 742 and 510 c.c.; the night specimens to 202 and 315 c.c. To interpret the increased frequency of voiding urine at night as signifying a nocturnal polyuria, as is often done, would in such cases lead to an erroneous conclusion.

In the course of these studies,[12] the impression has been gained that nycturia is frequently one of the earliest symptoms of renal disease

5. Quincke: Arch. f. exper. Path. u. Pharmakol., 1913, xxxii, 211.
6. Von Leube: Deutsch. Arch. f. klin. Med., 1869, v, 372.
7. Runeberg: Deutsch. Arch. f. klin. Med., 1880, xxvi, 211.
8. Wilson: Lancet, London, 1889, I. (67th year), 1299.
9. Iljisch: München. med. Wchnschr., 1896, xciii, 1299.
10. Laspeyres: Deutsch. Arch. f. klin. Med., 1900, lxviii, 175.
11. Pehu: Rev. de méd., 1903, xxiii, 379.
12. In collecting separate night and day specimens, the precautions previously mentioned, that supper be taken three hours before the night urine collection is begun, that no food or fluid be allowed during the night, and that the night specimen be completed before breakfast is eaten, have been strictly observed throughout.

met with. It may be found when the only other signs of nephritis are a trace of albumin and a few hyalin casts. Thus, in W. (Medical No. 34121), a laborer of 23 years, showing a trace of albumin and a moderate number of hyalin and granular casts in the urine, but no other signs of nephritis, the figures shown in Table 13 were obtained after the test meal:

TABLE 13.—Nephritic Test Meal in an Individual with a Slight Grade of Albuminuria, a Few Casts, but No Other Signs of Nephritis

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	65	1.020				
10-12	67	1.021				
12- 2	90	1.020				
2- 4	126	1.019				
4- 6	146	1.015				
6- 8	172	1.013				
Total day	666	.....	0.64	4.26	1.05	6.99
Night, 8-8	660	1.011	0.52	3.43	0.71	4.69
Total 24 hours	1,326	.....	....	7.69	....	11.68
Intake	1,760	.....	....	8.50	....	13.40
Balance	+ 434	.....	....	+ 0.81	....	+ 1.72

Impression: The concentration of urine, as indicated by the specific gravity and the percentage figures of sodium chlorid and nitrogen, are satisfactorily high. The total amounts of fluids and solids eliminated may also be considered normal. However, the urinary volume and specific gravity do not vary after the ingestion of meals as they should, and the night urine shows a distinct nocturnal polyuria with a low specific gravity. The whole picture, therefore, represents a moderately impaired renal function.

Occasionally, nocturnal polyuria is found in cases in which no organic cause for this phenomenon can be determined. It may be that in these patients an augmented night urine represents a functional change which exhibits itself as the first symptom of a kidney lesion. This is a surmise, and can be proved only by noting the subsequent course of events. One such case is as follows:

S. C. (Medical No. 33538), aged 38, a valet, has had several attacks of acute gout. The patient's joints show signs of the process, which has left permanent damage in the knees and some of the smaller joints of the feet; the urine is

TABLE 14.—Data in a Case of Nocturnal Polyuria Without Demonstrable Renal Involvement

Night Urine			Night Urine		
Specimen No.	Vol. c.c. of Night Urine	Sp. G. of Night Urine	Specimen No.	Vol. c.c. of Night Urine	Sp. G. of Night Urine
1	347	1.026	6	692	1.017
2	664	1.018	7	550	1.025
3	980	1.011	8	990	1.016
4	680	1.020	9	1,214	1.014
5	961	1.015			

negative for albumin and casts; the systolic blood pressure is 123; the phenolsulphonephthalein excretion is 80 per cent. in two hours. No signs of nephritis can be detected, though the frequent association of gout and damage to the kidney are kept in mind. The test meal shows a normal function, except for a nocturnal polyuria. This is duplicated on subsequent nights and the figures in Table 15 are obtained.

With the exception of the first specimen, the volume at night is distinctly increased above the normal (400 c.c.). The specific gravity (except in Specimen 3) is, however, not as low as is usual in pathological night urines. It may well be that in the very earliest stages of diminished renal function the amount of urine is increased without a lowering of the specific gravity. This also goes to show that the low specific gravity need not necessarily follow on the passage of a large volume of urine at night, but depends to some extent on other factors.

TABLE 15.—VOLUME, SPECIFIC GRAVITY AND NITROGEN PERCENTAGE OF THE NIGHT URINE IN CASES OF CHRONIC INTERSTITIAL NEPHRITIS *

Night Urine			Night Urine		
Volume c.c.	Specific Gravity †	Per Cent. Nitrogen	Volume c.c.	Specific Gravity †	Per Cent. Nitrogen
1,273	09	0.28	550	10	0.63
1,140	07	0.20	546	12	0.65
1,140	10	0.43	546	17	0.68
1,110	10	0.61	520	13	0.63
1,080	07	0.23	510 ‡	18	1.05
1,010	10	0.42	505	15	0.55
965	11	0.65	446 ‡	20	1.08
935	10	0.50	445	10	0.50
875	10	0.55	445	10	0.72
870	11	0.15	435	16	0.51
790	10	....	425 ‡	17	0.97
770	15	0.57	415	15	0.76
715	16	0.71	395	14	0.68
704	11	0.47	370	13	0.55
690	13	0.57	360	11	0.87
660	11	0.71	355 §	24	0.93
654	13	0.57	293 §	28	1.04
590 ‡	20	1.30	144	19	0.87
559	12	0.92	94	15	0.51
557	13	0.70			

* Includes all cases of chronic interstitial nephritis studied, many of them associated with hypertension and arteriosclerosis, but not complicated by myocardial insufficiency, a febrile process, marked anemia, or other intercurrent affection.

† Last two figures only.

‡ These cases may be considered as approaching the normal; from the night urine alone, only a very slight degree of impairment of renal function is evident.

§ Normal night urines; both of these cases are taken up in detail further on.

Besides the actual increase in the volume of night urine, changes in the specific gravity and concentration of nitrogen have proved themselves of importance in indicating impaired renal function. In Table 15 a considerable number of instances are given in which the night urine is normal in amount, or approximates the normal, and yet the

specific gravity findings are low and the concentration of nitrogen does not reach the normal.

It is a well established fact that nitrogen derived from the food is excreted rather slowly,[13] hence the quantity of nitrogen found in the night urine is disproportionately high. This has been shown to be

TABLE 16.—Types of Cases Other Than Chronic Interstitial Nephritis, Whose Urine Gives Evidence of Abnormal Nocturnal Excretion

	Night Urine		
	Volume c.c.	Specific Gravity *	Per Cent. Nitrogen
1. Chronic diffuse nephritis during			
(a) Water Retention (edema formation)	595	16	0.93
	553	16	0.62
	367	20	0.88
	270	30	....
	106	28	....
(b) Elimination of edema	960	11	....
	960	10	0.47
	950	14	0.73
(c) Water balance (edema eliminated)	865	13	0.75
	490	14	1.01
	400	17	1.17
2. Heart disease during			
(a) Myocardial decompensation	275	21	1.85
	172	21	1.67
	119	25	1.82
	91	20	1.68
(b) Elimination of edema	1,340	11	0.51
	990	13	0.56
	850	10	0.28
	720	07	0.35
(c) Water balance (edema eliminated)	520	14	0.84
	515	11	0.53
	438	12	0.67
3. Hypertensive nephritis, complicated by myocardial decompensation	815	18	0.94
	546	17	0.68
	435	16	0.51
	405	18	1.07
	350	19	1.12
	108	18	1.09
4. Severe anemia	1,250	10	0.51
	680	10	0.52
	256	11	0.57
	180	16	0.39
5. Cystitis and hypertrophied prostate gland	1,395	09	0.43
	1,146	10	0.35
	775	11	0.44
6. Pyelonephritis	950	10	0.45
7. Polycystic kidney	1,290	10	0.45
8. Diabetes insipidus	594	07	0.20

* Last two figures only.

13. Lusk: The Science of Nutrition, 1909, p. 120.

constantly above 1 per cent. in normal subjects, whereas, in Table 15, it is seen how low it has a tendency to become in cases of chronic nephritis, even when there is no nocturnal polyuria. The value of the specific gravity determinations in the night urine depends on similar principles of loss of power of concentration on the part of the diseased kidney.

Similar disturbances in nocturnal urinary secretion are seen in other conditions besides chronic interstitial nephritis. The list of these diseases is a considerable one (Table 16), and a consideration of them leads to the conclusion that renal function may be impaired, so far as the night urine is concerned, by a variety of factors. These same influences also modify the diurnal character of the urine, and they can be discussed to the greatest advantage in taking up the test meal as an entity.

THE RESULTS WITH COMPLETE NEPHRITIC TEST MEALS

Chronic Interstitial Nephritis (Primary or Secondary Contracted Kidney).—It must be borne in mind in studying renal function by means of a test meal or other procedure that anatomical lesions and changes in physiological activity of the organ need not parallel one another. This is particularly true of incipient nephritis; in advanced stages, when much of the renal parenchyma has been destroyed, divergence between autopsy findings and functional tests or clinical symptoms are far less marked. When only a limited amount of functionating renal tissue remains, the reserve power of the kidney and thus its ability to vary its activity within wide limits, is obviously restricted. It becomes necessary for such quantitatively reduced kidneys to function constantly at their maximum capacity, with the result that the urines secreted scarcely vary in their characteristics from day to day or even from hour to hour.

Examining the test meals of these advanced cases (Table 17, Chart 7), the hyposthenuria, as exhibited in the almost absolute fixation of the percentage figures for salt and nitrogen concentration and the specific gravity (Table 6) show under what continual strain the kidney is laboring to eliminate a sufficient quantity of solids. Even through polyuria it cannot keep pace with the food intake (Table 12). A still greater degree of retention, coupled with a more dilute urine, is seen in Chart 8 (Table 18). Many instances were obtained similar to the former, but only one more marked case of renal insufficiency has thus far been encountered, and that is the one pictured here (Chart 8). Both of these patients died within a few weeks after the test was taken, and the same bad prognosis proved itself correct whenever a test meal curve of this nature was produced. The points

indicating renal insufficiency in these severe examples of contracted kidney are the following:

1. Markedly fixed and low specific gravity.
2. Diminished output of both salt and nitrogen.
3. Tendency to total polyuria.
4. Night urine showing slight or marked increase in volume; low specific gravity; low concentration of nitrogen.

TABLE 17.—Reaction to Nephritic Test Meal in Advanced Hypertensive Nephritis

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	133	1.010	0.36	0.48	0.35	0.47
10-12	176	1.009	0.36	0.63	0.34	0.60
12- 2	156	1.010	0.32	0.50	0.35	0.55
2- 4	212	1.009	0.36	0.76	0.34	0.72
4- 6	164	1.009	0.38	0.62	0.36	0.59
6- 8	104	1.010	0.33	0.34	0.33	0.34
Total day	945	.....	....	3.33	....	3.27
Night, 8-8	590	1.010	0.34	2.01	0.38	2.24
Total 24 hours	1,535	.....	....	5.34	....	5.51
Intake	1,510	.....	....	5.80	....	12.20
Balance	— 25	.....	....	+ 0.46	....	+ 6.69

Impression (the figures correspond with Chart 7): Reaction to the nephritic test meal in a case of advanced hypertensive nephritis. There is very marked fixation of the percentage figures for nitrogen and salt concentration and the specific gravity. There is evident nitrogen retention. The salt intake is too low to make it certain that a diminished ability to excrete salt does not exist.

TABLE 18.—Extreme Interstitial Nephritis

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	24	1.005				
10-12	106	1.006				
12- 2	82	1.007				
2- 4	83	1.008				
4- 6	0	.....				
6- 8	230	1.008				
Total day	525	.....	0.12	0.63	0.25	1.28
Night, 6-8	1,140	1.007	0.12	1.37	0.20	2.27
Total 24 hours	1,665	.....	....	2.00	....	3.55
Intake	1,850	.....	....	6.00	....	13.00
Balance	+ 185	.....	....	+ 4.00	....	+ 9.45

Impression (the figures correspond with Chart 8): Reaction to the nephritic test meal in a case of extreme interstitial nephritis. Note the low fixed specific gravity, the retention of salt and nitrogen, and the night urine, which is increased in amount, shows a low specific gravity and a low nitrogen concentration.

Tracing the progress from the normal towards this ultimate stage, patients are found in whom a nocturnal polyuria persists, and yet there is no demonstrable affection of any kind in the kidney. Obser-

vations on such a case have been previously given in this paper. It is probable that these are the signs of a beginning nephritis exhibiting itself by slight changes in function. On the other hand, normal functional tests may be obtained when albumin and a few hyalin casts exist in the urine and there is a slight rise in blood pressure. An example of this kind is shown in Table 19, Chart 4, where the only

TABLE 19.—Comparatively Normal Renal Function in Early Hypertensive Nephritis

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	60	1.018				
10-12	140	1.009				
12- 2	156	1.016				
2- 4	58	1.022				
4- 6	252	1.013				
6- 8	122	1.010				
Total day	788	.....	0.52	4.10	0.52	4.10
Night, 8-8	355	1.024	0.71	2.51	0.93	3.30
Total 24 hours	1,143	.....	....	6.61	....	7.40
Intake	1,760	.....	....	8.50	....	13.40
Balance	+ 617	.....	....	+ 1.89	....	+ 6.00

Impression (the figures correspond with Chart 4): Except for a diminished nitrogen output and a slightly lowered nitrogen concentration at night, the response to this nephritic test meal is normal. It indicates a comparatively normal renal function in an early case of hypertensive nephritis.

TABLE 20.—Early Hypertensive Nephritis

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	465	1.009	0.51	2.37	0.34	1.58
10-12	102	1.014	0.62	0.63	0.77	0.79
12- 2	205	1.009	0.32	0.66	0.44	0.90
2- 4	160	1.010	0.28	0.44	0.64	1.02
4- 6	116	1.014	0.48	1.55	0.80	0.92
6- 8	160	1.006	0.09	0.14	0.29	0.46
Total day	1,208	.....	....	4.79	....	5.67
Night, 8-8	935	1.010	0.33	3.08	0.50	4.67
Total 24 hours	2,143	.....	....	7.87	....	10.34
Intake	1,760	.....	....	7.50	....	13.40
Balance	— 383	.....	....	— 0.37	....	+ 3.06

Impression (the figures correspond with Chart 5): The nephritic test meal shows a tendency toward fixation of specific gravity and a distinct nocturnal polyuria in an early case of hypertensive nephritis.

sign of diminished function exists in the slightly lowered concentration of nitrogen (0.93 per cent. at night instead of a normal of 1 per cent. or higher), and a moderate nitrogen retention. These changes are so slight as to make it doubtful whether it is not best to classify this

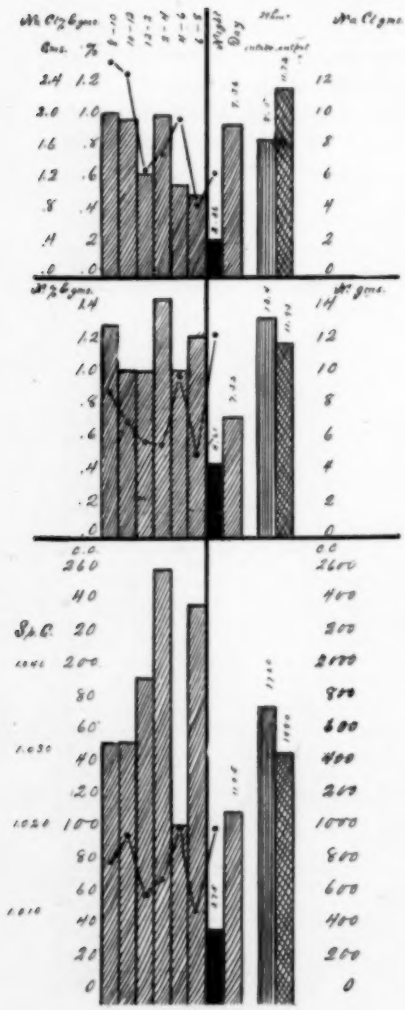


Chart 1

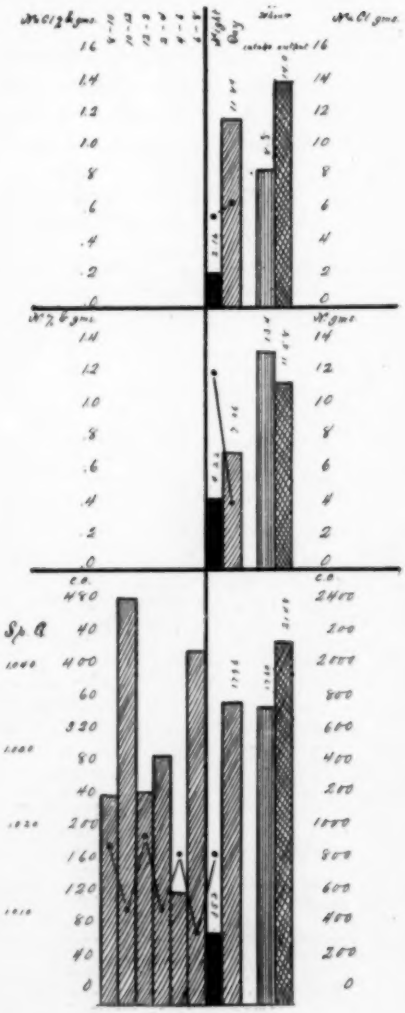


Chart 2

Chart 1.—Normal. Note the variations in specific gravity, high specific gravity and high concentration of nitrogen at night, and approximately normal water, salt and nitrogen output.

Chart 2.—Normal. Same as Chart 1, except that in this case polyuria is evident. This is probably due to the reaction in an individual who is used to a bland diet and not to the quantities of salt and purins given with the nephritic test meal.

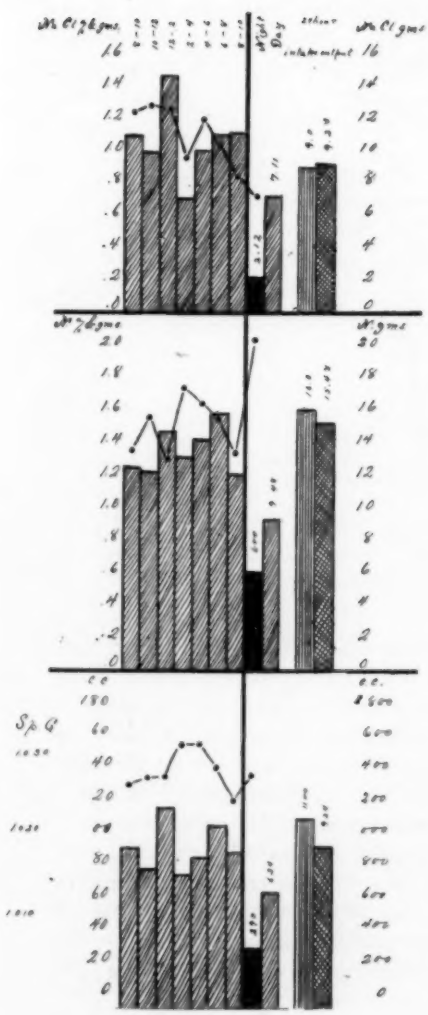


Chart 3

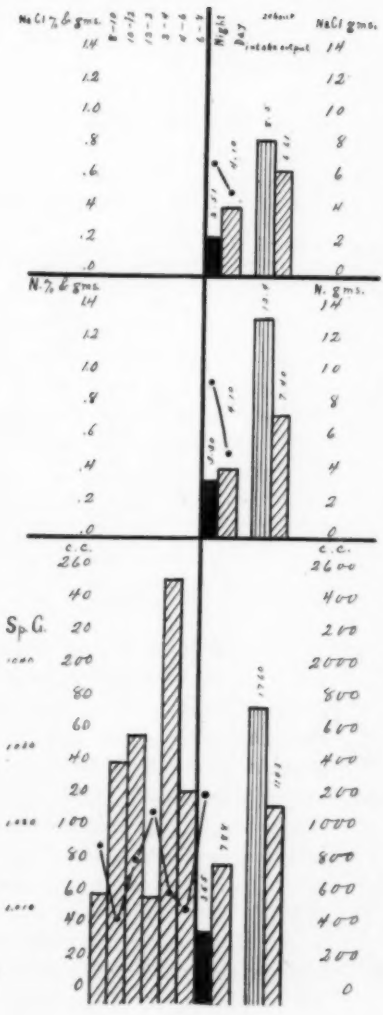


Chart 4

Chart 3.—Normal. Showing the effect of diminished fluid intake.

Chart 4.—Early case of hypertensive nephritis. (Systolic blood pressure 180, when up and about; 145 after rest in bed. Urine shows a trace of albumin and a few hyaline casts.) Nephritic test meal is normal, except for a slight grade of nitrogen retention.

test as a completely normal one, especially as the variations in specific gravity in the two-hourly specimens are marked; there is a good response of water excretion to dinner and supper, the salt elimination is adequate, and the night urine shows neither increased amount nor lowered specific gravity. Successive advances in impairment of renal function are seen in the tests depicted in Table 20, Chart 5, and in Table 21, Chart 6.

TABLE 21.—HYPERTENSIVE NEPHRITIS

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	172	1.019	0.95	1.63	1.01	1.74
10-12	154	1.020	0.99	1.52	0.87	1.34
12- 2	124	1.020	0.84	1.04	0.51	0.63
2- 4	110	1.020	0.74	0.81	0.93	1.03
4- 6	152	1.021	0.85	1.29	0.62	0.93
6- 8	143	1.020	0.72	1.03	1.11	1.59
Total day	855	.....	....	7.32	....	7.26
Night, 8-8	446	1.020	0.97	4.33	1.08	4.82
Total 24 hours	1,301	.....	....	11.65	....	12.08
Intake	1,760	.....	....	8.50	....	13.40
Balance .....+	459	.....	....	—3.15	....	+ 1.32

Impression (the figures correspond with Chart 6): Nephritic test meal in a case of marked hypertensive nephritis. The fixation of specific gravity at a level somewhat higher than that seen in more advanced cases of hypertensive nephritis is very striking.

In the former of these, the specific gravity fluctuates between narrower limits than normal, there is distinct polyuria, the night urine is increased in amount and shows a low specific gravity and low nitrogen concentration. In the second case, the fixation of specific gravity is striking, though its level is higher (1.020) than that seen in the more advanced stages of the disease (1.010). This phenomenon is not commonly seen in nephritic individuals, and when it does occur, the possibility of renal congestion, depending on myocardial decompensation, must be kept in mind. However, the oliguria, coupled with a very low salt output and a high nitrogen excretion in cardiac cases, usually distinguishes such urines from one another without difficulty. The changes that are brought about in the urine by the functional impairment occurring in the course of development of an interstitial nephritis may be formulated in the following manner, though this order of events will not pertain in every case. In the main, it portrays facts as they are usually encountered:

1. Nocturnal polyuria (over 400 c.c.).

2. Tendency to total polyuria (the volume of urine equals or surpasses the quantity of liquids ingested).

3. Fixation of specific gravity, gradually becoming more intense, until it is absolute and the specimens only show a maximum variation of 1 or 2 degrees. In the earlier stages, specific gravity may be fixed at a higher level than later.

4. Fixation of the two-hourly quantities of urine eliminated. That is, the usual polyuric response to meals is absent.

5. The quantity of night urine may diminish to within normal limits. Such night urines, however, are characterized by a low specific gravity and a low percentage of nitrogen.

6. A retention of both salt and nitrogen, which may become very marked.

Cases Simulating the Mode of Urinary Output Found in Advanced Nephritis.—In cases of hypertrophied prostate and its sequelae, of pyelonephritis, polycystic kidney and severe anemia, whether of the primary or secondary type, results are obtained with the test meal which are similar in every detail to those that have been described for advanced instances of contracted kidney. These are shown in Charts 9, 10, 11 and 12.

These observations make it clear that the low fixed specific gravity, etc., so characteristic of advanced cases of hypertensive nephritis may be reproduced by widely different causes. These may be summarized as follows:

1. Causes in the urinary passages, pyelitis, cystitis, hypertrophied prostate.

2. Causes in the blood; marked anemia.

3. Causes in the kidney itself (organic as well as functional lesions), pyelonephritis, polycystic kidney, chronic interstitial nephritis (both primary and secondary contracted kidney), diabetes insipidus.

It is true that changes resembling those mentioned above are found in congestion of the kidney and in chronic diffuse nephritis (before the picture of contracted kidney supervenes), although there are certain variations from the type just depicted that are of material aid in diagnosing and treating these cases that will be detailed a little further on. It is interesting to note how very different the influences are that result in similar changes in function. From the functional change alone one would be warranted in considering the prognosis grave. Hence it must be emphasized that, when such evidence of functional damage is obtained, searching examination must be made for extrarenal causes or curable renal lesions, especially a hypertrophied prostate or other cause for urinary obstruction. Prognosis and therapy will depend largely on the cause of the functional impairment, not on its degree. The removal of a hypertrophied

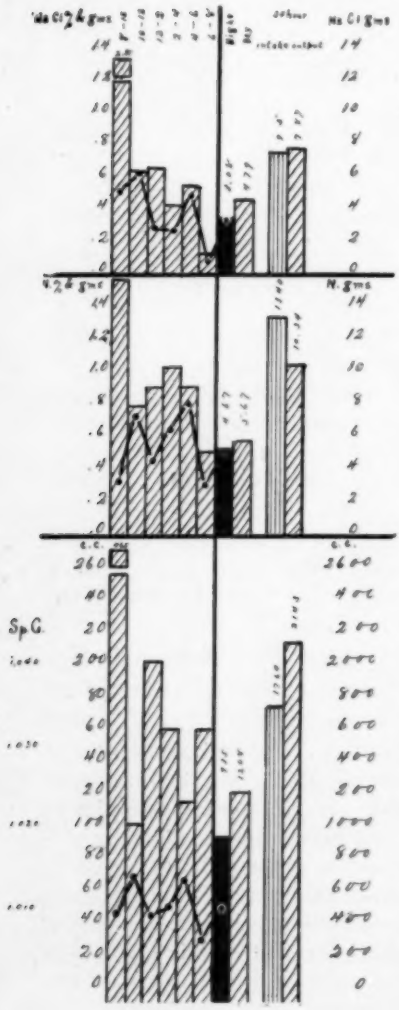


Chart 5

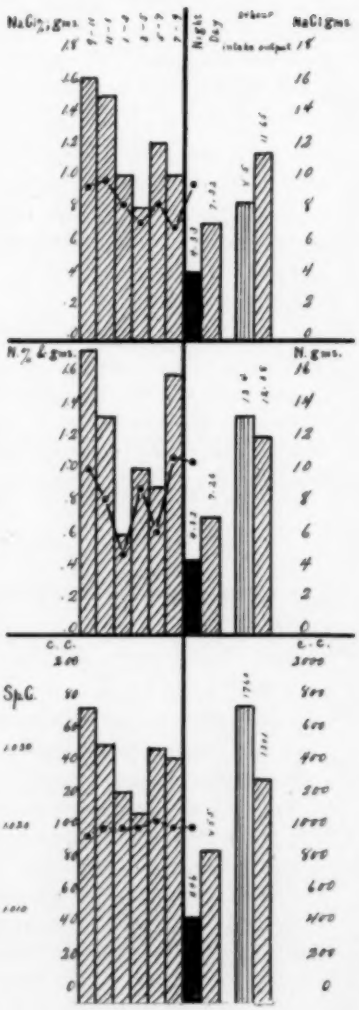


Chart 6

Chart 5.—Early case of hypertensive nephritis. (Systolic blood pressure, 160-190. Urine shows faint trace of albumin and a few granular casts.) Nephritic test meal here shows a tendency towards the fixation of specific gravity and distinct nocturnal polyuria.

Chart 6.—Marked hypertensive nephritis. (Blood pressure, 180. Urine shows trace of albumin and a few hyaline casts.) Nephritic test meal shows markedly fixed specific gravity at a somewhat higher level than the more extreme cases shown in Charts 7 and 8.

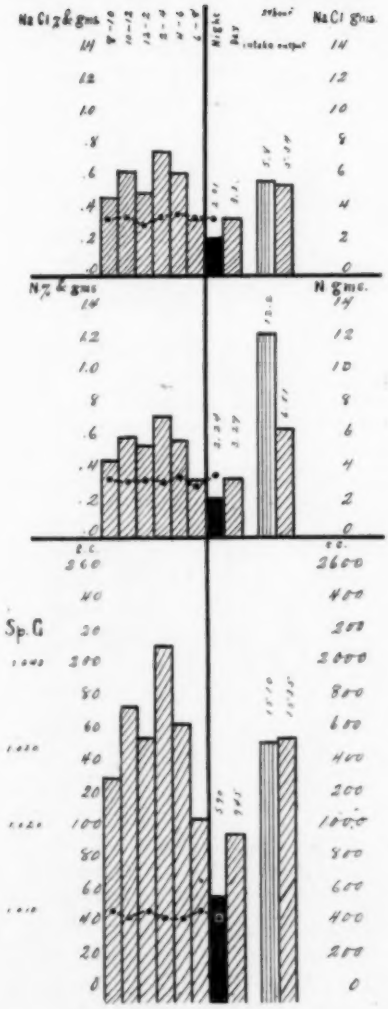


Chart 7

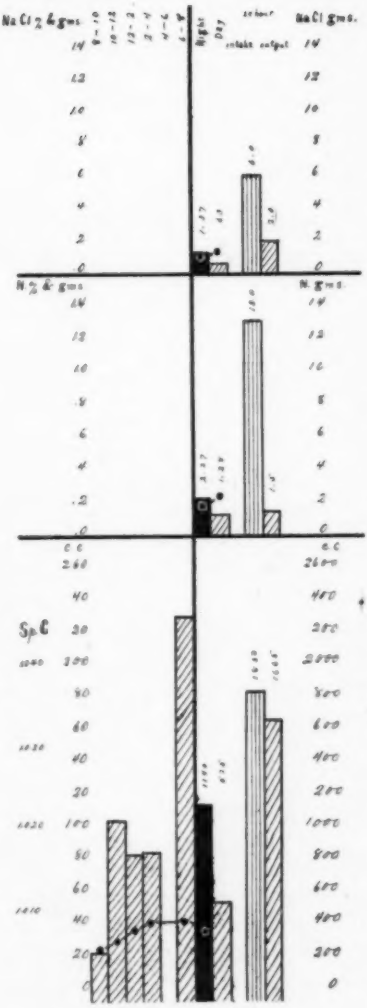


Chart 8

Chart 7.—Advanced hypertensive nephritis. (Systolic blood pressure in the neighborhood of 200. Albumin to 3 gm. per liter; few granular and hyaline casts; albuminuric retinitis.) Nephritic test meal shows markedly fixed specific gravity at the level of about 1.010 and marked fixation of the percentage quantities of salt and nitrogen. This test was repeated on two subsequent occasions and exactly the same figures obtained. There is evidently a retention of salt and nitrogen, low specific gravity and a low concentration of nitrogen at night with only slight nocturnal polyuria.

Chart 8.—Extreme hypertensive nephritis. (Systolic blood pressure, 200-235. Urine contains trace of albumin and a few granular casts). Nephritic test meal accentuates all the conditions found in Chart 7 to an extreme degree.

prostate, the subsidence of a pyelitis, the cure of a severe anemia, may be followed by great functional improvement, while a similar test meal picture in chronic nephritis or polycystic kidney would indicate a speedy fatal termination.

Renal Congestion (*Myocardial Insufficiency*).—With extreme acute myocardial decompensation very characteristic results are obtained with the test meal (Table 22, Chart 13):

1. Specific gravity markedly fixed at the level of about 1.020.

2. A diminished output of salt. The low percentage figures for sodium chlorid are striking.

3. An adequate nitrogen output. The very high concentration of nitrogen is in marked contrast to that of the salt.

4. An oliguria.

5. A night urine normal in character.

The oliguria, good nitrogen excretion, normal night urine and high fixed specific gravity readily distinguish this condition from the advanced cases of chronic interstitial nephritis.

The same characteristics as those shown above are found in the patients with myocardial insufficiency persisting over a long period (Table 23, Chart 14). Similar results are also obtained in those cases in which insufficient heart action may be considered to be "slight," that is, when it is only manifested by dyspnea on exertion or slight cyanosis. Thus, in this class of patients, since the kidney is so sensitive in its reaction to circulatory disturbances, the test meal becomes a valuable means of estimating the degree of myocardial insufficiency which may exist.

TABLE 22.—URINE IN EXTREME CARDIAC DECOMPRESSION

	Urine		Sodium Chlorid		Nitrogen	
Time of Day	c.c.	Sp. Gr.	Per Cent.	gm.	Per Cent.	gm.
8-10	61	1.018	0.20	0.12	1.52	0.93
10-12	52	1.020	0.24	0.12	1.83	0.95
12- 2	65	1.019	0.26	0.17	1.73	1.12
2- 4	55	1.018	0.27	0.15	1.65	0.90
4- 6	30	1.020	0.26	0.07	1.61	0.48
6- 8	35	1.021	0.40	0.14	1.80	0.63
Total day	298	.....	....	0.77	....	5.01
Night, 8-8	275	1.021	0.31	0.85	1.85	5.07
Total 24 hours	573	.....	....	1.62	....	10.08
Intake	570	.....	....	5.00	....	12.00
Balance .....—	3	.....	....	+ 3.38	....	+ 1.92

Impression (the figures correspond with Chart 13): Nephritic test meal in an extreme case of cardiac decompensation. Note the high concentration of nitrogen as compared to the low figures for salt. There is distinct oliguria. (The water output should be higher as general anasarca was present.)

TABLE 23.—URINE IN MARKED CARDIAC DECOMPENSATION

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	65	1.025				
10-12	53	1.024				
12- 2	51	1.024				
2- 4	49	1.025				
4- 6	37	1.024				
6- 8	57	1.021				
Total day	312	.....	0.58	1.81	1.53	4.77
Night, 8-8	172	1.021	0.42	0.72	1.67	2.87
Total 24 hours	484	.....	....	2.53	....	7.64
Intake	995	.....	....	7.00	....	9.40
Balance .....+	511	.....	....	+ 4.47	....	+ 1.76

Impression (the figures correspond with Chart 14.) Nephritic test meal in an individual with marked cardiac decompensation which has persisted for some time. The same results as in Table 19 may be noted.

Hypertensive nephritis complicated by myocardial decompensation is a symptom complex met with so frequently that it demands attention in a study of this kind. Table 24, Chart 19, shows the results of a test on a case of this sort. It is very apparent that in this instance the characteristics of myocardial decompensation are more in evidence than those of hypertension or nephritis. In other words, the congestion proves itself the predominating factor in influencing renal activity. This is of interest in connection with von Noorden's[4] statement of the variability of the specific gravity in chronic interstitial nephritis, in contrast with the usual conception of low, fixed specific gravity under these circumstances. Low salt, contrasted with high nitrogen concentration and a rather high specific gravity in the urine of patients with a systolic blood pressure in the neighborhood of 200 and marked cardiac insufficiency, has been demonstrated in five cases. However, instances have also been met with in which the effects of the passive congestion cannot "break through" the barrier imposed by the contracted kidney. One example of this kind was found in M. C., aged 50, a valet, whose systolic blood pressure varied between 235 and 180; the heart was the seat of an aortic insufficiency of luetic origin, and gave evidences of marked dilatation and hypertrophy; there were signs of extreme cardiac decompensation, marked edema, fluid in the pleural and peritoneal cavities, intense dyspnea and cyanosis. The cardiac and renal diagnoses were confirmed at necropsy. The immediate cause of death in this case was evidently passive congestion, resulting from weak heart action, and yet the specific gravity of the daily specimens of urine in the course of thirty-six days varied between 1.012 and 1.014, with the exception of one occasion, when it rose to 1.019.

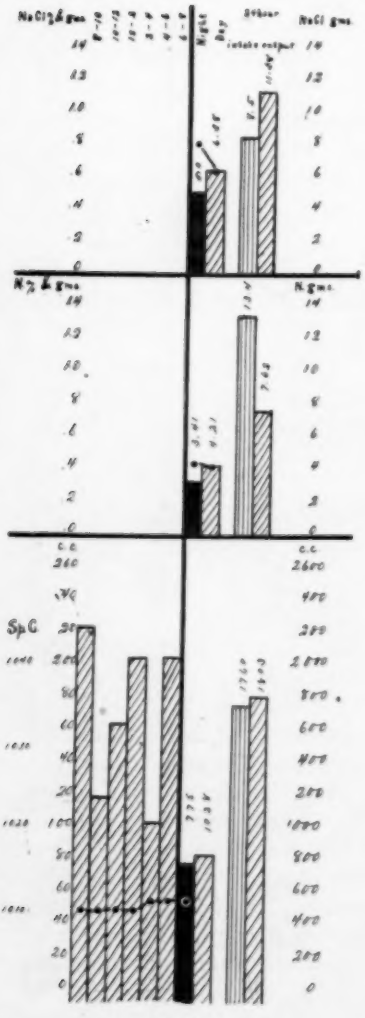


Chart 9

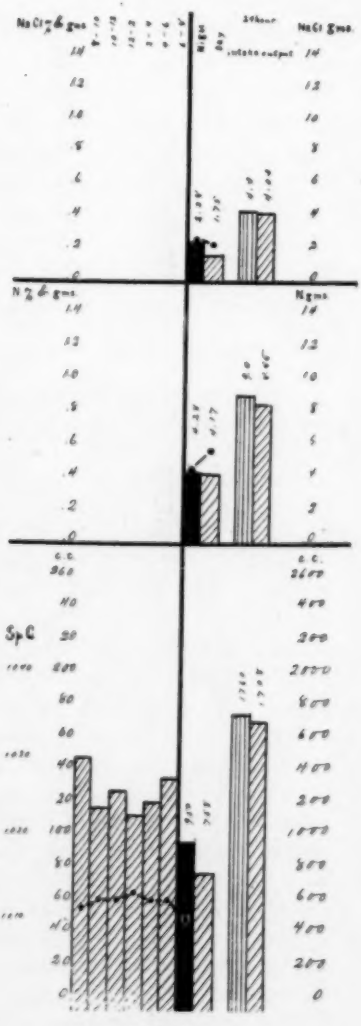


Chart 10

Chart 9.—Cystitis; pyelitis; hypertrophied prostate.
Chart 10.—Pyelonephritis.

Chart 11

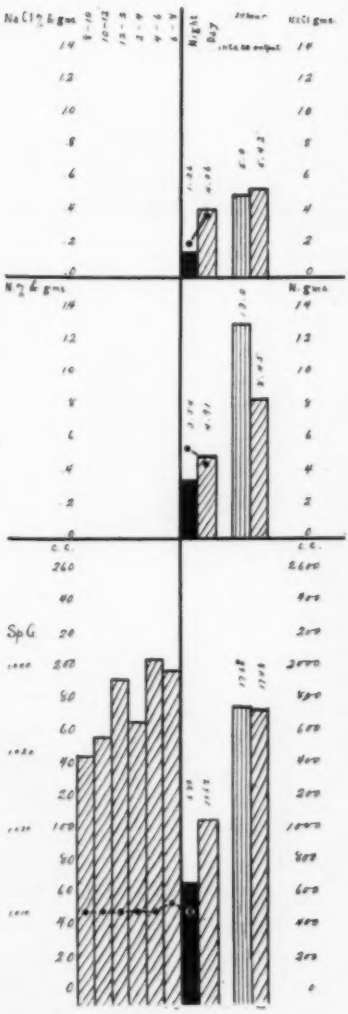


Chart 12

Chart 11.—Polycystic kidney.

Chart 12.—Marked anemia. Hb., 44 per cent.; red blood cells, 2,240,000.

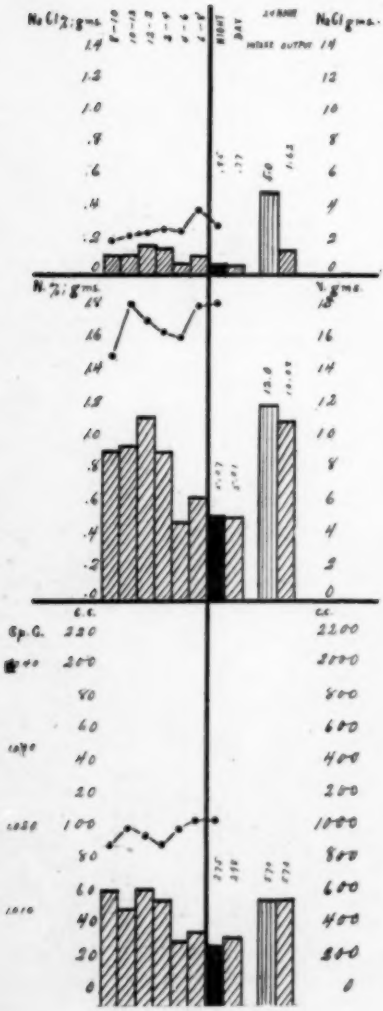


Chart 13

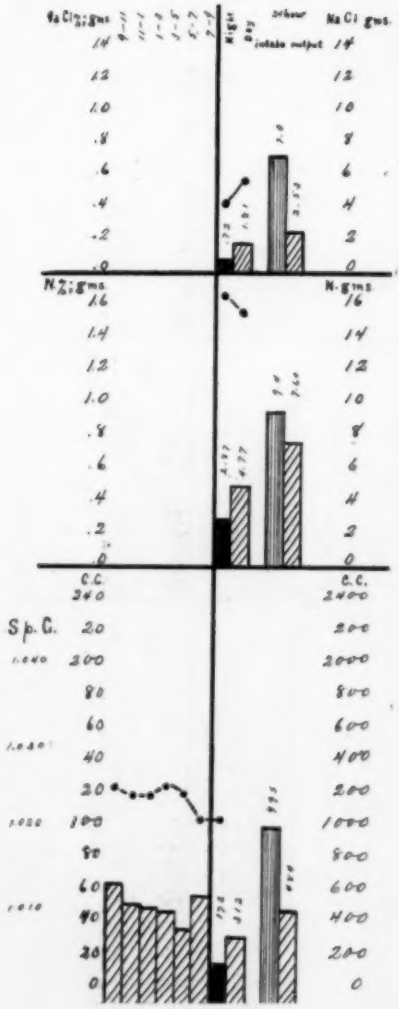


Chart 14

Chart. 13.—Extreme cardiac decompensation. Nephritic test meal shows a low water output with a fixed specific gravity at about 1.020. (The water output should be higher, as general anasarca was present.) The nitrogen percentage is extremely high and nitrogen elimination is adequate. There is a retention of salt and a very low concentration of salt in the urine.

Chart 14.—Marked cardiac decompensation. Nephritic test meal shows the same changes as Chart 13, but to a less degree.

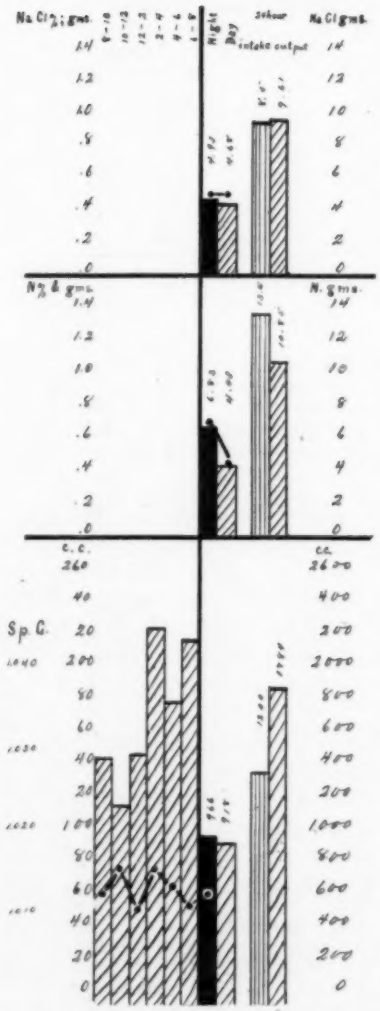


Chart 15

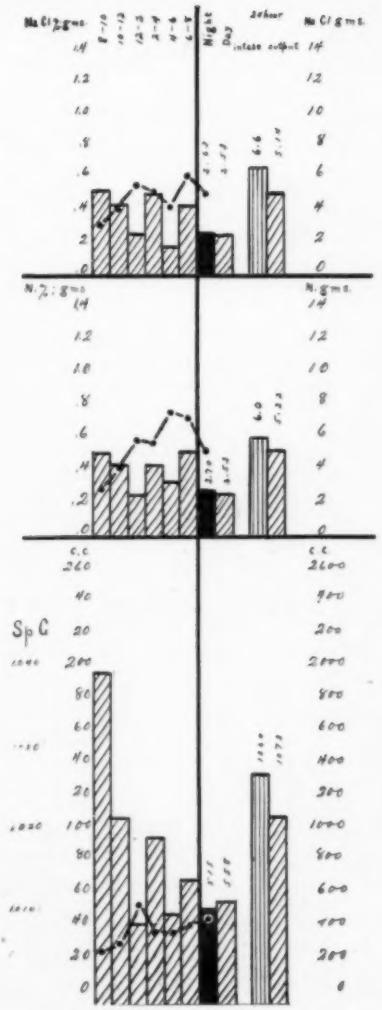


Chart 16

Chart 15.—Cardiac decompensation while eliminating edematous fluid. Nephritic test meal shows a low specific gravity, nocturnal polyuria and low specific gravity at night. Salt and nitrogen eliminations are normal.

Chart 16.—Myocardial insufficiency — after an apparently complete restoration to normal condition. Nephritic test meal shows a low, rather fixed specific gravity, a slight grade of nocturnal polyuria and a very low specific gravity in the night urine.

TABLE 24.—Hypertensive Nephritis Complicated by Myocardial Insufficiency

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	85	1.016	0.41	0.34	1.09	0.93
10-12	83	1.017	0.31	0.26	1.14	0.94
12- 2	100	1.017	0.41	0.41	1.04	1.04
2- 4	100	1.017	0.41	0.41	1.04	1.04
4- 6	106	1.016	0.46	0.49	0.92	0.98
6- 8	80	1.020	0.35	0.28	1.16	0.92
Total day	554	.....	....	2.19	....	5.85
Night, 8-9	405	1.018	0.10	0.40	1.07	4.33
Total 24 hours	959	.....	....	2.59	....	10.18
Intake	1,375	.....	....	7.50	....	8.80
Balance .....+	416	.....	....	+ 4.91	....	— 1.38

Impression (the figures correspond with Chart 19): Test meal curve in a case of hypertensive nephritis complicated by myocardial insufficiency. The low salt and high nitrogen elimination are characteristic of renal congestion, as is the high fixed specific gravity. It shows how the influence of renal congestion may "break through" the functional picture presented in hypertensive nephritis.

It becomes apparent that when the combination of cardiac insufficiency and hypertensive nephritis exists, the urinary symptoms of either may predominate. In the experience presented here, the characteristic urine of a passively congested kidney has been most often found. However, the number of cases studied is too small to insist on this point. Krehl,[14] on the other hand, believes that under these circumstances, in spite of renal congestion, the specific gravity of the urine is low and its volume high.

After cardiac compensation has again become established in cases of uncomplicated heart disease, the urinary curve of the test meal is much changed. During the period of elimination of edema (Table 25, Chart 15), as might be expected from the polyuria existing at this time, the following characteristics are found:

1. Specific gravity low and somewhat fixed.
2. Nitrogen elimination normal.
3. Salt and water excretion exceed the amount ingested.
4. The night urine is increased in amount, has a low specific gravity and low percentage of nitrogen.

Subsequently, all the edematous fluid having been eliminated, the urinary function does not assume the normal type, as is usually supposed, but exhibits certain decided peculiarities (Table 26, Chart 16):

1. Low, moderately fixed specific gravity.
2. Normal nitrogen and water output.

14. Krehl: Die Erkrankungen d. Herzmuskels, 1913, p. 448.

3. Slightly diminished salt excretion.

4. The night urine may or may not be increased in quantity; its specific gravity and nitrogen concentration are low.

TABLE 25.—Cardiac Decompensation Recovery, Eliminating Edema

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	142	1.012				
10-12	114	1.015				
12- 2	144	1.010				
2- 4	224	1.015				
4- 6	178	1.013				
6- 8	216	1.010				
Total day	1,018	.....	0.51	4.68	0.44	4.03
Night, 8-8	966	1.012	0.51	4.93	0.71	6.82
Total 24 hours	1,984	.....	....	9.61	....	10.85
Intake	1,230	.....	....	8.50	....	13.40
Balance	—754	.....	....	—1.11	....	+2.55

Impression (the figures correspond with Chart 15): Nephritic test meal from a case of cardiac decompensation while eliminating edema fluid. Note the low and rather fixed specific gravity, the elimination of large amounts of salt and fluid and a night urine increased in quantity with a low specific gravity and a low percentage of nitrogen.

TABLE 26.—Full Cardiac Compensation Following Decompensation

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	198	1.005	0.27	0.54	0.27	0.53
10-12	108	1.006	0.42	0.45	0.41	0.44
12- 2	41	1.011	0.58	0.24	0.60	0.24
2- 4	95	1.009	0.54	0.51	0.59	0.43
4- 6	46	1.009	0.43	0.20	0.79	0.36
6- 8	70	1.010	0.61	0.43	0.74	0.52
Total day	558	.....	....	2.37	....	2.52
Night, 8-8	515	1.011	0.51	2.63	0.53	2.70
Total 24 hours	1,073	.....	....	5.00	....	5.22
Intake	1,360	.....	....	6.60	....	6.00
Balance	+287	.....	....	+1.60	....	+0.78

Impression (the figures correspond with Chart 16): Nephritic test meal from an individual with full cardiac compensation following a period of decompensation. The figures show considerable deviation from the normal: low, moderately fixed specific gravity, slightly diminished salt output, nocturnal polyuria with a low specific gravity and low concentration of nitrogen.

This abnormal picture persists for a period of weeks and possibly months, and seems to be a distinct indication that damage has been caused to the kidney by passive congestion which does not disappear immediately when normal circulation is resumed. The urine passed during this period resembles that of advanced interstitial nephritis in many respects, and in observing the low specific gravity from day to day, the clinician is often puzzled in deciding whether such a nephritis really exists or not.

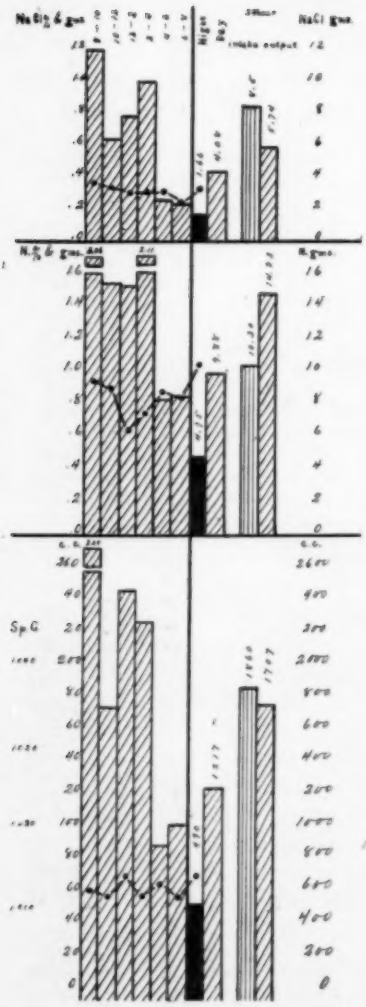


Chart 17

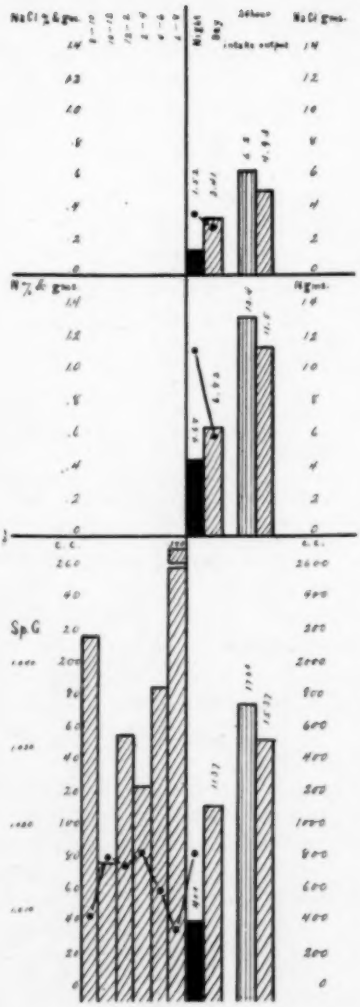


Chart 18

Chart 17.—Chronic diffuse nephritis, with slight hypertension. (Systolic blood pressure, 164 to 174; considerable amount of edema; urine shows a marked amount of albumin, blood, granular and hyaline casts.) Nephritic test meal shows an advanced degree of involvement of renal function, very much as in Chart 7, except that the nitrogen elimination is not reduced.

Chart 18.—Same case as on Chart 17 after an interval of about a month, when the blood pressure had returned to normal, the red blood cells had disappeared from the urine and the edema eliminated. Nephritic test meal shows a condition which approaches the normal and reflects the clinical improvement of the patient when compared with Chart 17.

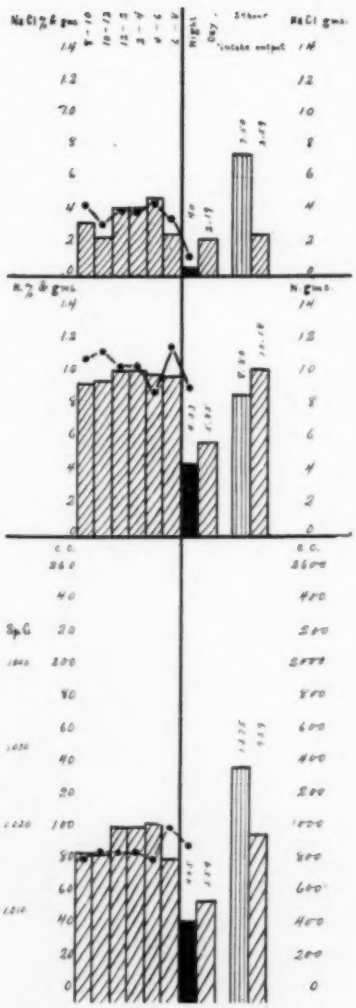


Chart 19

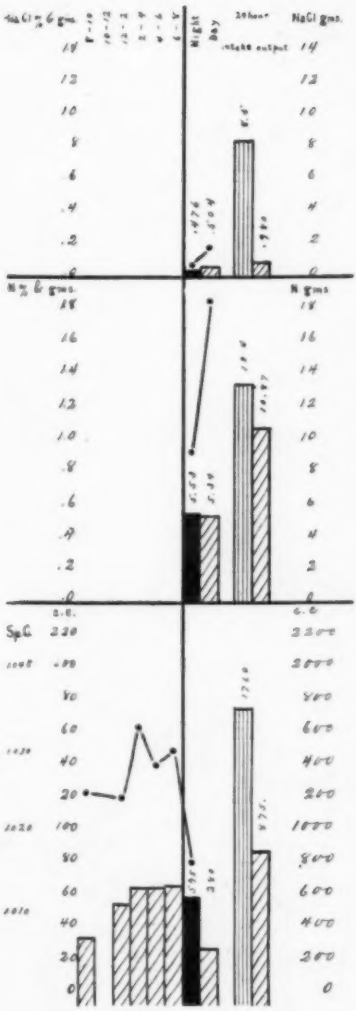


Chart 20

Chart 19.—Myocardial insufficiency, combined with secondary hypertensive nephritis. (Systolic blood pressure, 190 to 230. Marked albuminuria, with many granular casts.) Nephritic test meal shows a result which is decidedly more characteristic of renal congestion than it is of a fairly well advanced nephritis. (Compare with Charts 7 and 13.)

Chart 20.—Chronic diffuse nephritis. Nephritic test meal shows marked salt retention, low specific gravity and low concentration of nitrogen *at night*, slight nocturnal polyuria and water retention.

Chronic Diffuse (Parenchymatous) Nephritis.—The urinary findings in nephritis of this type are as variable as the clinical symptoms. At times, clinical and functional tests are in strict accord with one another, and at others they diverge widely. During the period of edema formation, the test meal (Table 27, Chart 20) shows marked salt and water retention, a nocturnal polyuria and a good nitrogen excretion. Such urines bear a great resemblance to those seen in myocardial decompensation, and, in fact, it is at times absolutely impossible to differentiate between the two conditions from these data without having recourse to the physical signs, etc., which usually make the diagnosis an easy one.

While edema is being eliminated, the test meal again shows a marked similarity to cases of passive congestion under the same circumstances. Thus, in Table 28 (compare with Table 25, Chart 15), the amount of urine eliminated is large, the quantity of salt excreted approximates double the intake, and nocturnal polyuria is marked.

TABLE 27.—CHRONIC DIFFUSE NEPHRITIS

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	32	1.025				
10-12	0	.....				
12- 2	54	1.024				
2- 4	64	1.033				
4- 6	64	1.028				
6- 8	66	1.030				
Total day	280	.....	0.18	0.50	1.91	5.34
Night, 8-8	595	1.016	0.08	0.48	0.93	5.53
Total 24 hours	875	.....	....	0.98	....	10.87
Intake	1,760	.....	....	8.50	....	13.40
Balance .....+	885	.....	....	+7.52	....	+2.53

Impression (the figures correspond with Chart 20): Nephritic test meal in a case of chronic diffuse nephritis during the period of edema formation. The marked salt and water retention, the nocturnal polyuria and high nitrogen excretion are characteristic.

TABLE 28.—CHRONIC DIFFUSE NEPHRITIS

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	230	1.022	1.16	2.66	1.15	2.64
10-12	130	1.025	1.08	1.40	1.42	1.85
12- 2	118	1.022	1.01	1.19	1.21	1.43
2- 4	136	1.022	1.14	1.44	1.25	1.70
4- 6	96	1.020	0.70	0.68	1.18	1.13
6- 8	108	1.014	0.80	0.87	0.89	0.96
Total day	818	.....	....	8.24	....	9.71
Night, 8-8	950	1.014	0.78	7.61	0.73	7.14
Total 24 hours	1,768	.....	....	15.85	....	16.85
Intake	1,760	.....	....	8.50	....	13.40
Balance .....—	8	.....	....	—7.35	....	—3.45

Impression: Results of the nephritic test meal in a case of chronic diffuse nephritis, while eliminating edema. Note the large amounts of fluid, salt and nitrogen excreted.

TABLE 29.—CHRONIC DIFFUSE NEPHRITIS

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	328	1.012	0.36	1.18	0.93	3.06
10-12	174	1.011	0.32	0.65	0.88	1.53
12- 2	248	1.014	0.30	0.76	0.64	1.52
2- 4	279	1.011	0.32	0.98	0.76	2.11
4- 6	88	1.013	0.32	0.28	0.92	0.81
6- 8	100	1.011	0.23	0.23	0.85	0.85
Total day	1,217	.....	....	4.08	....	9.88
Night, 8-8	490	1.014	0.34	1.66	1.01	4.95
Total 24 hours	1,707	.....	....	5.74	....	14.83
Intake	1,860	.....	....	8.50	....	10.30
Balance	+153	.....	....	+2.76	....	—4.53

Impression (the figures correspond with Chart 17): Nephritic test meal in a case of chronic diffuse nephritis. A marked involvement of renal function is evident from the low fixed specific gravity.

TABLE 30

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per Cent.	Sodium Chlorid gm.	Nitrogen Per Cent.	Nitrogen gm.
8-10	216	1.009				
10-12	75	1.016				
12- 2	156	1.015				
2- 4	124	1.017				
4- 6	186	1.012				
6- 8	380	1.007				
Total day	1,137	.....	0.30	3.41	0.60	6.82
Night, 8-8	400	1.017	0.38	1.52	1.17	4.68
Total 24 hours	1,537	.....	....	4.93	....	11.50
Intake	1,760	.....	....	6.20	....	13.40
Balance	+223	.....	....	+1.27	....	+1.90

Impression (the figures correspond with Chart 18): Nephritic test meal from the same case as in Table 29. This test was performed about one month later and the marked clinical improvement is reflected in the result which approaches the normal very closely.

An advanced degree of involvement of renal function is seen in Table 29, Chart 17. This is indicated by the low, fixed specific gravity during the night and day time. After rest in bed and other therapeutic measures, the clinical aspect of this case had improved markedly, and in studying Table 30, Chart 18, it is seen that this improvement is reflected in a test meal which approximates the normal. The ability of the patient to excrete salt is not well brought out in these tests. In the first, there was salt retention, in the second, there was not. This would have been proved had all the salt offered been taken, since in the early observations recorded it was shown that during the

first period the salt excretion represented the maximum effort of the kidney in this direction, even when more salt was added to the diet, while in the second it did not. Such pitfalls as these must be considered in the interpretation of the nephritic test meals, but with a little care they may usually be avoided.

One of the most interesting results obtained in this work has been the occasional occurrence of cases showing many of the symptoms of nephritis and little or no change from the normal response to the test meal. (The converse was noted in the cases mentioned under nocturnal polyuria). The following was an instance of this kind:

J. C. (Medical No. 33921), a salesman, aged 47, comes to the hospital complaining of headache; the systolic blood pressure varies between 185 and 200 mm. of mercury; there is considerable cardiac hypertrophy, the apex impulse being in the sixth intercostal space, 13 cm. to the left of the median line; otherwise, the heart shows no abnormalities; the urine contains a trace of albumin and a few hyaline and granular casts. The test meal (Table 31) shows no abnormalities of note. This indicates that the constitutional symptoms of the nephritic complex are well advanced, but that the kidney, so far as its function is concerned, is scarcely affected. Such facts are not only of interest from the pathological point of view, but also of extreme importance in prescribing proper dietary and other therapeutic measures.

TABLE 31.—Normal Test Meal Curve in Marked Hypertensive Nephritis

	Urine		Sodium Chlorid		Nitrogen	
Time of Day	c.c.	Sp. Gr.	Per Cent.	gm.	Per Cent.	gm.
8-10	220	1.017				
10-12	170	1.016				
12- 2	154	1.020				
2- 4	182	1.018				
4- 6	106	1.019				
6- 8	34	1.025				
Total day	866	.....	0.50	4.33	0.66	5.72
Night, 8-8	283	1.028	0.48	1.41	1.04	3.05
Total 24 hours	1,159	.....	....	5.74	....	8.77
Intake	1,350	.....	....	8.50	....	9.80
Balance .....+	191	.....	....	+ 2.76	....	+ 1.03

Impression: An approximately normal test meal curve in a case of marked hypertensive nephritis. It shows how, in isolated instances, renal function may be normal in spite of extensive lesions characteristic of interstitial nephritis.

SUMMARY

The nephritic test meal, as suggested by Hedinger and Schlayer, and elaborated in this paper, has not only proved itself to be an admirable test for renal function, but also in many cases has been of great value in diagnosing cardiac, renal and other conditions. Much pleasure and profit may be derived from a study of diseases of the kidney from this point of view, since it forms a basis for a rational therapy and a stimulus towards keener clinical observation.

The test is a qualitative one of the mode of urinary function as measured by the specific gravity, salt, nitrogen and water excretion in two-hourly periods during the day, and for a twelve-hour period at night. The normal individual yields specimens with specific gravity figures which vary ten points or more from the highest to the lowest, a night urine high in specific gravity, 1.018 or more, high in its percentage of nitrogen—above 1 per cent.—and small in amount—400 c.c. or less. The quantities of water, salt and nitrogen excreted approximate the intake. When kidney function becomes involved, the first signs are usually demonstrated in the night urine, the quantity becomes increased; the specific gravity and the nitrogen concentration are lowered. One or all of these changes from the normal may occur. In severe cases of chronic nephritis, an advanced degree of functional inadequacy of the kidney is indicated by a markedly fixed and low specific gravity, a diminished output of both salt and nitrogen, a tendency to total polyuria and a night urine showing an increased volume, low specific gravity and low concentration of nitrogen. Such functional pictures, however, are not confined to nephritis. They are found regularly in many other conditions: pyelitis, cystitis, hypertrophied prostate, marked anemia, pyelonephritis, polycystic kidney, and diabetes insipidus. The cause of diminished renal function, it is clear, must be sought for in many directions—the urinary passages, the blood or the kidney itself. Prognosis and therapy will depend largely on the cause of the fundamental impairment and not on its degree. A divergence between the degree of functional renal involvement and the intensity of the signs and symptoms of nephritis is frequently found, and accentuates the lack of parallelism that there may be between functional and anatomical lesion.

In chronic diffuse (parenchymatous) nephritis, the condition of renal function is characterized by its variability. In these instances, the results of the test meal have proved to be extremely valuable in giving an idea of the status of salt, nitrogen and water excretion, besides the picture of renal efficiency as a whole. The findings in myocardial insufficiency vary according to the activity of the heart. Distinct differences are found with myocardial decompensation and the accumulation of edema, the period of eliminating edema, and subsequently, when cardiac compensation is again fully established, it requires some time before the kidney resumes its normal activity. This intervening period is indicated by a tendency to a low, fixed specific gravity and a nocturnal polyuria. During the period of full

myocardial decompensation the results of kidney activity are very characteristic, the specific gravity is markedly fixed at the level of about 1.020, the salt output is diminished, that of nitrogen is high, in marked contrast to the salt, and there is oliguria. When chronic nephritis and cardiac decompensation coexist, as they so often do in hypertensive nephritis, the urine may exhibit the characteristics due to either lesion. The determining factor is probably to be found in the chronic nephritis which may or may not be so far advanced as to present an unchanging barrier to the influence of renal congestion.

Johns Hopkins Hospital.

THE DIFFERENTIATION OF CEREBRAL AND CARDIAC TYPES OF HYPERARTERIAL TENSION IN VASCULAR DISEASE*

A CLINICAL STUDY

WILLARD J. STONE, M.D.
TOLEDO, OHIO

THE PHYSICAL CONCEPTION OF BLOOD PRESSURE

It is not sufficiently recognized, I believe, that the measurement of systolic pressure alone gives but incomplete evidence of the state of circulatory tension. Other data seem essential to an understanding of the condition, such as the constant or diastolic pressure existing between systoles and the actual head, or pulse pressure, forcing the blood column toward the periphery.

In a previous article[1] I have endeavored to establish a conception of the subject from the standpoint of dynamics and statics. In this conception the diastolic pressure represents potential energy, since the blood column exerts energy of position and not motion during diastole. During systole, when the intraventricular pressure equals or slightly exceeds the diastolic pressure in the aorta, the aortic valves open. The pressure of a given volume of blood leaving the left ventricle must, however, be considerably in excess of the diastolic pressure in order to force the blood toward the periphery. Therefore when systole occurs, the pressure exerted by the left ventricle, in order to force a volume of blood into already filled vessels, must be in excess of the pressure existing in those vessels. The transfer of energy, producing motion of the blood column, through systole of the left ventricle, must therefore be in the form of kinetic energy, which is the energy of motion. The excess of kinetic energy, as manifested by the systolic pressure over the potential energy manifested by the diastolic pressure, represents the pulse pressure or the head of pressure useful to the movement of the blood column.

It thus appears that the study of blood pressure in a given patient becomes a problem in dynamics and statics. The systolic pressure is a variable force, since it depends on the amount of kinetic energy expended for circulatory requirements at a given time. The diastolic pressure represents the less variable or constant force; its variability depending, with a given volume of blood, on the degree of contraction

* Submitted for publication June 23, 1915.

1. Stone, W. J.: Jour. Am. Med. Assn., 1913, lxi, 1256.

and elasticity of the arterial walls. It is the sum of the diastolic and pulse pressures which make up what has been recognized clinically as the systolic pressure.

In the beginning of sphygmomanometry, attention was largely directed to the measurement of the systolic pressure, a condition of affairs which largely obtains today after more than a decade of experience. The belief may be expressed that the entire conception of blood pressure will undergo a change when it is generally understood that the diastolic is as important as the systolic pressure in an understanding of circulatory tension. If this is important from the diagnostic standpoint, it is quite as important from the prognostic point of view. A large majority of patients with hypertension fall into either the *cerebral* or the *cardiac* group. It therefore becomes a matter of importance to determine, so far as possible, in which group a patient belongs, since advice and treatment appropriate to postpone the dangers of the one might not be appropriate to postpone the dangers of the other condition.

THE AUSCULTATORY METHOD

Both pressures are most accurately taken by auscultation, with a stethoscope of the disk type, over the brachial artery on the inner aspect of the arm below the compressing arm band. Korotkoff[2] first described this method in 1905. In applying this method, compression is made in the arm band to a point above which all sound is heard in the artery. The air pressure is then gently released and as the pressure falls, the point at which the first sound is heard, is taken as the systolic pressure. A series of similar clear sounds are then heard (the first phase) which are soon replaced by a series of murmurs (the second phase). The murmurs are then replaced by a second series of clear sounds (the third phase). These clear tones are shortly replaced by dull tones (the fourth phase). Korotkoff believed that the diastolic pressure corresponded to the dull tone following the third phase. Ettinger[3] expressed the same belief in 1907. Lang and Manswetona in 1908[4] and Warfield in 1912[5] have also expressed the belief, founded on experimental evidence, that the point of transition from clear to dull tones following the third phase, i. e., the fourth phase, accurately corresponded to the diastolic pressure. This has been corroborated by Taussig and Cook.[6]

2. Korotkoff: Mitt. d. k. mil. med. Akad. zu St. Petersburg, 1905, xi, 365.
3. Ettinger: Wien. klin. Wchnschr., 1907, xx, 992.
4. Lang and Manswetona: Deutsch. Arch. f. klin. Med., 1908, xciv, 441.
5. Warfield, L. M.: THE ARCHIVES INT. MED., 1912, x, 258.
6. Taussig and Cook: THE ARCHIVES INT. MED., 1913, xi, 542.
7. Hooker and Southworth: THE ARCHIVES INT. MED., 1914, xiii, 384.

Latterly, Hooker and Southworth,[7] using the Erlanger instrument in combination with the method of Einthoven and Geluk for recording brachial sounds, have expressed the opinion that for clinical purposes the cessation of sounds in the artery (the fifth phase) corresponds with the diastolic pressure. This point has been on the average from 2 to 4 mm. lower than the fourth phase in my series of cases. I have preferred to follow in this series of cases the opinion of Warfield, Taussig and Cook, and Ettinger, in whose experimental work there seemed but little chance for error. I am inclined, however, to believe, with further experience, that in perhaps the majority of decompensated cardiac lesions the transition from the third to the fourth phase is exceedingly difficult to determine. In such instances I have taken as the diastolic pressure a reading from 2 to 4 mm. above the point at which the pulse sound disappeared. It would undoubtedly simplify the procedure if the point of disappearance of pulse sound was taken as the diastolic pressure. Further experience will probably show the wisdom of adopting this point, since for all practical accuracy it answers the purpose. The systolic pressure by the auscultatory method is about 5 mm. higher than by palpation, but since the former method is so much more accurate in the determination of both systolic and diastolic pressures, it should entirely supplant the latter more commonly used method.

THE HEART FORCE OR LOAD

From the clinical standpoint there can be no doubt that some means of estimating cardiac work as a circulatory force founded on pressure variations would be desirable. Strassburger[8] first attempted in 1905 to obtain a blood pressure quotient by dividing the pulse pressure by the systolic pressure, or P.P./S.P.

Tigerstedt[9] has also suggested this formula for determining the efficiency of the heart as a pump. The velocity of the arterial stream divided by the work of the heart gives, according to him, the efficiency of the heart as a pump. His formula is expressed as follows:

$$\frac{\text{Pulse pressure} \times \text{pulse rate} = \text{velocity}}{\text{Systolic pressure} \times \text{pulse rate} = \text{work}} = \text{Heart efficiency.}$$

$$\text{This is equivalent to } \frac{\text{Pulse pressure}}{\text{Systolic pressure}}$$

It has been shown by many writers that either the pulse pressure multiplied by pulse rate, or the systolic pressure multiplied by pulse

8. Strassburger: Quoted by Barach and Marks, THE ARCHIVES INT. MED., 1914, xiii, 648.

9. Tigerstedt: Quoted by Hirschfelder, Diseases of the Heart and Aorta, 1910, p. 26.

rate, does not give an adequate idea of the volume output of blood from the heart. Nor is there any reason for believing that the velocity of stream divided by cardiac work, as expressed in this formula, measures heart efficiency. As mentioned below, in circulatory shock *the heart rate increases out of all proportion to the full pulse pressure,* owing to the central vasomotor influence, and the heart may be doing greatly increased work with lessened output owing to stasis in the splanchnic area. The cardiac efficiency is therefore impaired while its work is increased.

In addition, this formula appears to me objectionable for the following reasons: When the intraventricular pressure rises in systole the aortic valves do not open until the pressure equals the diastolic pressure in the aorta. The ventricular pressure, up to this point, does not avail the circulation anything at all, it being the force or pulse pressure exerted by the myocardial contraction in excess of the diastolic pressure which moves the blood column. The ratio of this pressure to the diastolic pressure should therefore be taken as the measure of work done by the myocardium in moving the column of blood.

In a study[1] of 170 patients reported in 1913 it was found that in 75 normals of various ages the average diastolic pressure was 80 mm., and that the pulse pressure was an additional 40 mm., making the systolic pressure 120 mm. The normal pulse pressure or force required to effect mass movement of blood was therefore 40/80 or 50 per cent. more than the pressure required to open the aortic valves; that is, 50 per cent. more pressure or force was required than the diastolic pressure. This represented a ratio or heart load which may be expressed as follows, *pulse pressure divided by diastolic pressure* or P.P/D.P. A load of 50 per cent. was considered to be the approximate normal, which represented the fact that a pressure 50 per cent. in excess of the diastolic pressure was necessary to effect movement of blood toward the periphery. The ratio may vary within normal limits between 40 and 60 per cent. During the past year about 200 normal individuals have been examined and the above ratio between pulse pressure and diastolic pressure has been found to hold true in fully 90 per cent. of the cases.

I am aware that such, or any ratio, is open to certain objections, for by any method of clinical estimation of pressure in the brachial artery, it is difficult to say with certainty what conditions may exist in the remainder of the circulatory tree. In fact, it is entirely conceivable that with normal pressures in the brachial, stasis may be present in the splanchnic vessels to so marked a degree as seriously to lower the diastolic pressure without seriously affecting the systolic

pressure, although seriously affecting the output of blood moved by the heart contraction. "The cardiac output is entirely dependent on the venous pressure," as Crile has stated. From the cardiac standpoint we are not so much concerned with the output of blood moved by the cardiac muscle as with cardiac work performed, which is an entirely different matter. Increased work does not necessarily mean increased output of blood moved, nor does decreased work necessarily mean decreased output. The heart may be pumping into more or less empty vessels in shock due to venous stasis in the splanchnic area and be doing greatly increased work, with corresponding increase in the pulse pressure, but with lessened output of blood from the left ventricle; for with lowered venous pressure on the right side of the heart, the output of blood would, of course, be lowered on the left side.

Since shock may be considered to result in venous splanchnic stasis, the diastolic pressure is decreased, but the force used causing pulse pressure is increased, a fact in accord with the observation of Hürthle "that with a decreased peripheral resistance there is an increase in the pulse pressure." The heart is then doing increased work, but with lessened output. This is shown in the following history: In a patient with a flank stab wound lacerating the kidney cortex, with severe retroperitoneal hemorrhage and peritonitis from puncture of the colon, the systolic pressure was 98, the diastolic 55, and the pulse pressure 43; the heart load ratio was 78 per cent. during the hemorrhage. After drainage of the abdomen and enteroclysis, the diastolic fell to 38 while the pulse pressure was increased to 54 (systolic 92), the heart load ratio was 142 per cent. Shortly before death from peritonitis and acute heart failure, the diastolic fell still further to 35 and the pulse pressure was increased to 75 (systolic 110); the heart load was 214 per cent. Such was the condition in an individual with a strongly acting heart.

On the contrary, with a weak myocardium exhausted by some acute illness, the pulse pressure, as well as the heart load ratio, that is, the force available to the movement of blood, is usually low; for example:

1. G. M., aged 37, streptococcus septicemia, with endocarditis, all valves apparently involved, pulse rate 120 to 140, subnormal temperature for two weeks before death. The systolic pressure varied from 85 to 100, the diastolic from 70 to 75, and the pulse pressure from 10 to 25. The average pulse pressure for three days before death was 20. The average heart load for this period was 23 per cent.

2. H. B., aged 54, abscess and gangrene of lung following pneumonia. The systolic pressure was 105, the diastolic 85 and pulse pressure 20. The heart load was 24 per cent. eight hours before death.

3. C. D., aged 24, postdiphtheritic pharyngeal paralysis, vagus paralysis (?). Pulse at wrist 36, over precordia 120, systolic pressure 90, diastolic 70, pulse pressure 20; the heart load was 28 per cent. twelve hours before death.

4. Mrs. R. A., aged 33, probable gastric ulcer, starvation and nephritis. The systolic pressure was 115, the diastolic 100, pulse pressure 15, the heart load was 15 per cent. An unfavorable surgical prognosis was given and the patient died two weeks later from inanition.

5. Mrs. P. L., aged 32, acute miliary tuberculosis with intestinal perforation, showed a systolic pressure of 120, diastolic 105, and pulse pressure of 15 twelve hours after the perforation. The heart load ratio was 14 per cent. Fourteen hours later the systolic pressure was 130, the diastolic 110, the pulse pressure 20, and the heart load 18 per cent. Eight hours later, with advancing general peritonitis, the systolic pressure was 145, the diastolic 110, the pulse pressure 35, and the heart load 32 per cent. Sixteen hours later (four hours before death) the systolic pressure was 98, the diastolic 85, the pulse pressure 13, and the heart load 15 per cent.

Barach and Marks[10] have recently criticized this method of estimating the percentage of cardiac force expended useful to the circulation, and while they concede that the greater number of normal cases do show the 50 per cent. ratio between the pulse pressure and diastolic pressure, they believe that there is a wide range below and above this mark in normal individuals. While such a condition may have existed in their series of young individuals susceptible to psychic influences (402 out of 552 patients were between the ages of 17 and 21 years) it should not invalidate the conclusion that an average working basis for normals can with advantage be compared with the conditions found to exist generally in pathologic circulatory conditions.

I now wish to direct attention to certain groups comprising the last 75 patients with circulatory disturbance whom I have examined. For convenience these patients have been classified as follows:

1. Hypertension (cerebral group).
2. Hypertension (cardiac group).
3. Myocardial and valvular lesions with increased heart-load ratio.
4. Myocardial and valvular lesions with decreased heart-load ratio.

HYPERTENSION (CEREBRAL GROUP)

In this group of 27 patients the average systolic pressure was 202, the diastolic pressure 134, and the pulse pressure 68. The heart-load was 51 per cent. The distinctive feature of this series was the high diastolic pressure with a heart-load ratio within normal limits, 40 to 60 per cent. In other words, with an increase in the diastolic pressure, the heart muscle showed compensatory ability to meet the increased demands by an increase in the pulse pressure, with the result that the heart-load percentage was within normal limits while at rest. The important point in this series is the high diastolic pressure as an index of the degree of arterial hypertension. The terminal event in such cases is usually cerebral hemorrhage or cerebral thrombosis and edema. Although an increased heart-load may coexist, it usually is

10. Barach and Marks: THE ARCHIVES INT. MED., 1914, xiii, 648.

not the important feature barring overstrain. This is shown in Case 9 of Table 1, in which the heart-load was 105/130 or 81 per cent. The morning on which this observation was taken this patient had suffered a hemiplegia. Her heart-load decreased under the enforced rest to normal 51 per cent. a few months later, but the diastolic pressure remained high, varying from 130 to 145.

Under the cerebral group are found many of those patients with high diastolic pressures and cerebral symptoms the terminal events of which have for many years been placed under the heading of uremia. They are usually placed under this heading because of the history of night polyuria, with urine of low specific gravity and the temporary or constant presence of albumin with tube casts. The exitus usually occurs in rapid or gradual coma under the title of uremia. The symptoms in such instances are those of cerebral thrombosis and edema, and as such should be so designated. There is no question that the kidneys present, in such cases, evidences of diffuse or interstitial changes and as such are seriously damaged as functionating organs, but it is comparatively rare to see such patients with chronically damaged kidneys die in anuria. The point is that the essential change involves the smaller blood vessels all over the body, and that the symptoms of the terminal event concern an edema of the brain as well as the kidneys. The kidney involvement is concomitant and not the essential change. As Janeway[11] has stated, "The most prominent symptoms associated with high blood pressure are circulatory rather than renal." He states also that there has been a marked tendency to return to the view of Gull and Sutton (1872) that the disease is primarily a disease of the smaller blood vessels. In fact, Richard Bright[12] in 1836, referred to some of the symptoms of nephritis as manifestations of "vascular disease," a term which may well be retained as descriptive of the symptom complex.

In Janeway's series of cases death occurred in the following order of frequency:

1. Gradual cardiac insufficiency.
2. With uremic symptoms.
3. Apoplexy.
4. Some complicating acute infection.
5. Angina pectoris.
6. Acute edema of the lungs.

It is probable that the first and sixth divisions of this group could be combined, since the symptoms of acute pulmonary edema rarely occur without evidences of myocardial exhaustion. It will thus be

11. Janeway, T. C.: THE ARCHIVES INT. MED., 1913, xii, 755.
12. Bright, Richard: Guy's Hosp. Rep., 1836, i.

TABLE 1.—Hypertension (Cerebral Group)*

No.	Name	Age	S. P.	D. P.	P. P.	Cardiac Load Per Cent.	
1	Miss E. K.	52	200	125	75	60	Fatigue and dyspnea on exertion; pressure in head, 11/25/13.
..	" " "	..	200	135	65	48	Trace albumin, 12/27/13.
2	Miss I. Y.	42	185	115	70	60	Retinal hemorrhage; plethora; urine neg.
3	Miss M.	25	175	110	65	60	Edema; decreased urinary output with albumin, 12.0 gm. per liter; acute exacerbation. Chronic diffuse nephritis. Death one year later.
4	Mrs. G. S.	49	210	135	75	56	360 c.c. urine in twenty-four hours; much albumin; chronic interstitial nephritis; death in coma due to cerebral edema.
5	F. O.	42	205	135	70	52	Angina; pressure in head; syncopal attacks, improved by venesection; urine previously contained albumin and casts; now negative.
6	Dr. S. T.	84	180	120	60	50	Cheyne-Stokes breathing intermittently; occasional extrasystole; thrombosis of ant. tibial artery.
7	Dr. W. W.	39	220	160	60	37	Comatose from cerebral hemorrhage; urine solid with albumin; death one week later.
8	Mrs. W. J.	56	180	130	50	38	Fatigue on slight exertion; dizziness; death one year later with gradually falling pressure in coma; symptoms of uremia due to cerebral edema.
9	Mrs. H. P.	62	235	130	105	81	Pain in arms; dyspnea on exertion; paroxysmal vertigo; slight hemiplegia; urine negative, 12/24/13.
..	" " "	..	220	145	75	51	Vertigo and mental confusion; urine negative, 9/12/14.
10	Mrs. E. B.	53	190	120	70	58	History of two slight apoplectic seizures with weakness of right arm and leg, also of headaches and dizziness. Urine contains much albumin; now loss of bladder and rectal control; systolic murmur over aorta; sudden death four months later.
11	M. G. B.	49	225	140	85	60	History of night polyuria. Urine contains albumin and sugar; heart shows systolic murmur at apex; ringing second aortic; gallop rhythm. Death seven months later; general and pulmonary edema.
12	J. H. P.	52	220	140	80	57	Headaches, mental confusion; earlier dyspnea, relieved by digitalis, 8/18/14.
..	.....	..	210	135	75	55	Urine, albumin positive. Specific gravity low; night polyuria, 9/28/14. Death in coma three months later; cerebral edema.
					50	35	Nocturnal headaches and polyuria; dizzi-

13	P. J. J.	54	190	140	50	35	Nocturnal headaches and polyuria; dizziness; urine contains much albumin; heart negative, except accentuated second aortic.
..	.....	..	225	160	65	40	Much vertigo, 2/26/15.
14	Mrs.R.G.S.	44	195	130	65	50	Vertigo on exertion; cardiac hypertrophy one inch to left; accentuated first tone at apex; urine negative.
15	J. W. D.	67	215	130	85	65	Complains of vertigo; systolic blow over aorta; urine negative.
16	Miss M. K.	50	225	130	95	73	Vertigo; fatigue; urine negative.
17	Mrs.L.E.C.	64	190	120	70	58	Syncopal attacks; angina; suffocation; systolic murmur apex; urine negative. Death one year later; angina pectoris, 10/13/14.
18	M. L. C.	69	195	135	60	44	Vertigo; accentuated second aortic; irregular and intermittent pulse.
19	C. B.	54	180	120	60	50	Much albumin and sugar in urine; polyuria (5,000 c.c. in twenty-four hours).
20	Gen.E.R.K.	72	200	120	80	66	Chronic nephritis; death one month later in coma with cerebral and pulmonary edema.
21	P. L.	38	205	135	70	51	Vertigo and headache; urine contains much albumin; nocturnal polyuria.
22	Mrs. K.	38	165	135	30	22	Acute exacerbation, chronic diffuse nephritis; blind before becoming comatose; cerebral edema; urine 1,000-1,200 c.c. in twenty-four hours; contains much albumin, five days before death.
23	Rev.E.M.A.	51	220	130	90	69	Mental confusion; failing memory; weakness; night polyuria; low specific gravity; much albumin; many casts.
24	J. P.	58	185	135	50	37	Dyspnea of sudden onset; edema of limbs; ascites; swollen liver; cyanosis; urine contains albumin; cardiac dilatation (?) Death one month later.
25	Mrs. M. G.	24	230	170	60	35	Evidences of nephritis for six years; facial paralysis of central origin; night polyuria; much albumin; many casts and blood cells.
26	Mrs. J. V.	60	195	150	45	30	Frequent subconjunctival and dermic hemorrhages; dyspnea on exertion; cardiac hypertrophy; systolic murmur loudest over aorta; marked accentuated second aortic; sclerosis arch aorta; myocardial fatigue. Urine 1.007; polyuria; albumin present.
27	J. H. T.	63	190	145	45	31	Urine negative in 1912; now complains of dyspnea due to emphysema and myocardial fatigue; indistinct heart tones; pulse rate 120 after slight exertion; urine contains much albumin.

* Average pressures in most instances.

seen that the two most common causes of death in hyperarterial tension are cardiac and cerebral. For convenience the following classification may be used:

- Death in hypertensive vascular disease
  - 1. Cardiac
    - 1. Myocardial exhaustion.
      - Dilatation. Acute pulmonary edema.
    - 2. Angina pectoris.
  - 2. Cerebral
    - 1. Thrombosis and edema associated with disturbed renal function.
    - 2. Hemorrhage.

Janeway has stated that the exact height of the blood pressure did not seem to have much bearing on life expectancy. This conclusion was based on evidence secured by systolic readings alone in probably the larger proportion of his cases. Every physician is familiar with the fact that some patients may live for many years with extremely high systolic pressures providing cardiac strain is avoided and due care is taken to secure adequate rest and proper elimination. Such a conclusion depends, however, not so much on how high the systolic pressure has become, but rather on the height of the diastolic pressure and the quality of stock in the arterial walls. Janeway's statement consequently needs modification. I am certain, speaking from the standpoint of hypertension, that an individual with a systolic pressure of 200 and a diastolic pressure of 140, is in greater danger of cerebral death than an individual with a systolic pressure of 200 and a diastolic pressure of 100. I am likewise certain that the individual with a systolic pressure of 200 and a diastolic of 90 to 100 is in greater danger of a cardiac death. It is apparently the constant high diastolic pressure rather than the intermittently high systolic pressure which predisposes to cerebral accident. If this were not true, cerebral death would occur much more frequently in the cardiac group of hypertension (see below), a condition which in my experience has rarely occurred, although the systolic pressures in many patients of the cardiac group were as high as the systolic pressures in those of the cerebral group. Records of the diastolic pressure become of importance, therefore, as an aid in prognosis and advice as to treatment.

In the cerebral hypertension group, the main symptoms were pressure in the head, vertigo, nocturnal headache, wearing off usually by noon, mental confusion, retinal and subconjunctival hemorrhages, fatigue on exertion and a history of nocturnal polyuria. Objectively, the urine may contain albumin, is of low specific gravity, the total quantity is increased, and periodically abundant casts are found. The radial and femoral arteries are rigid, the second aortic tone is ringing in character and a systolic murmur may be present at the apex, transmitted to the right toward the aorta. As before mentioned, the diastolic pressure is high, from 120 to 160, and if the individual has been

able to avoid undue exertion and has a compensating heart, the systolic pressure is high also. If cardiac dilatation has occurred, even though slight in degree, from some unusual exertion, the systolic pressure is lower, which with little change in the diastolic pressure, produces an altered ratio and a diminished heart-load percentage. This is illustrated in Case 24 of Table 1 and Case 1 of Table 4, in which cardiac deaths occurred in patients of the cerebral type. Generally, however, in the cerebral group, the death occurs from hemorrhage or with the symptoms of cerebral edema, usually designated uremia.

HYPERTENSION (CARDIAC GROUP)

Of the twenty-four patients in this group, the average systolic pressure was 180, the diastolic pressure 92, and the pulse pressure 88. The heart-load ratio was therefore increased from the normal of 50 per cent. to 96 per cent. The distinctive feature of this group was the low diastolic pressure as compared with the cerebral group. Most of these patients showed arterial hardening, but the contraction of the smaller blood vessels could not have been so marked or the diastolic pressures would have been increased. Practically all showed cardiac hypertrophy at some time in compensation, which had resulted not so much because of the increased peripheral resistance, but because of sclerotic damaged valves, coronary sclerosis, or as a result of extracardial factors, such as dilatation of the aortic arch, liver cirrhosis, gout, syphilis or hard physical labor, calling for unusual cardiac demands.

In the cardiac hypertension group, the main subjective symptoms were fatigue on exertion and dyspnea, anginoid pains in chest, edema of extremities and palpitation. Objectively, the heart was usually hypertrophied, the rate was in a number of instances of the perpetually irregular type, or was intermittent, due to extraventricular systoles; systolic murmurs were found in a number of instances over the base or apex, transmitted toward the aorta and into the vessels of the neck, pointing to sclerosis of the aorta. The second aortic tone was usually accentuated. *The urine was negative to albumin and casts in a large majority,* but the quantity was usually diminished. None of the patients in this series showed the nocturnal polyuria or symptoms of nephritis, so common among the patients in the cerebral hypertension group. The death occurs most frequently with the symptoms of a gradually failing heart muscle. The systolic pressure remains high until the heart muscle begins to fail and then gradually falls as the muscle tone diminishes (the so called "primary high, secondary low" sequence). One frequently encounters in the literature the statement that normal pressures are found to be present shortly before death in

TABLE 2.—Hypertension (Cardiac Group)

No.	Name	Age	S. P.	D. P.	P. P.	Cardiac Load Per Cent.	
1	Mrs. S. F.	78	150	80	70	87	Left arm and leg weakness for three months; cerebral embolism and softening; systolic murmur over aorta transferred to neck; sclerosis of arch.
2	Mrs. H. U.	57	190	108	82	69	Dyspnea; edema of ankles for years following rheumatism; apex in anterior axillary line; acute bronchitis; rate 136; temperature 101; perpetual arrhythmia.
3	Mrs.N.N.C.	70	160	70	90	128	Mitral stenosis and regurgitation moderate; periodic dyspnea; arteriosclerosis.
4	I. R.	77	170	100	70	70	Fatigue; hypertrophy left ventricle; emphysema.
5	Mrs.E.R.K.	66	185	95	90	94	Inspiratory dyspnea; anginoid pains in chest; cardiac hypertrophy.
6	Mrs. A. W.	72	205	115	90	78	Nocturnal dyspnea; fatigue on exertion; cardiac hypertrophy.
7	S. M. H.	81	170	85	85	100	Dyspnea on exertion; urine contains nucleo- and sero-albumin due to catheter life; no cerebral symptoms.
8	Mrs. E. B.	77	180	90	90	100	Secondary anemia; reds 2,500,000; systolic blow over base; urine negative; precordial distress; fatty heart.
9	G. P.	65	152	78	74	94	Fatigue on exertion; gout; sclerotic radials; intermittent pulse; hypertrophy left ventricle.
10	Mrs. C. G.	66	175	75	100	133	Dyspnea; cardiac asthma; marked irregularity due to extraventricular systoles; rate 60, 2/23/14.
..	.....	..	185	105	80	76	Much improved under digitalis and sodium iodid; rate 84, 3/9/14.
..	.....	..	160	60	100	166	Return of dyspnea, 4/26/14.
11	Mrs. F. W.	48	220	100	120	120	Sclerosis aorta; hypertrophy left ventricle; relative aortic insufficiency.
12	Mrs. McC.	71	195	105	90	85	Palpitation and irregularity; dyspnea on exertion, 1/6/13.
..	.....	..	195	90	105	117	Weakness and loss of weight, 6/23/13.
..	.....	..	165	75	90	120	Weakness and loss of weight, 7/23/13.
..	.....	..	170	90	80	88	Edema ankles; urine negative, 9/8/13.
..	.....	72	195	85	110	130	Vertigo and dyspnea, 9/14/14.

13	Mrs. M.S.	42	160	90	70	77	Perpetual arrhythmia; rate 112-116; murmurs over all valves; anascara; sudden death two and one-half months later, 10/8/13.
14	Mrs.S.A.J.	48	180	110	70	63	Obesity; fatty heart (?); systolic murmur over base and aorta; urine negative; edema of limbs to knees.
15	L. A.	67	160	90	70	77	Moderate dyspnea; systolic murmur over apex transmitted to aorta; sclerosis of; urine negative, although albumin and sugar had previously been present. Death six months later in coma; probably cerebral.
16	Mrs. M. D.	63	178	100	78	78	Dark spots before right eye; probably old retinal hemorrhage; heart negative except accentuated second aortic; urine negative.
17	Miss S. J.	55	210	110	100	90	Occasional tachycardia alternating with bradycardia; no syncopal attacks or vertigo; accentuated second aortic; urine negative.
18	Mrs. S. J.	40	175	100	75	75	Dyspnea and cough; presystolic and systolic murmur apex; accentuated second pulmonic; edema extremities; cyanosis lips in prone position.
19	C. W. E.	62	160	110	50	45	Vertigo and headaches; urine negative; systolic murmur apex transmitted to aorta; sclerosis of, perpetual arrhythmia; rate 56.
20	W. M.	67	170	80	90	112	Dyspnea, anginoid pains in chest and epigastrium; cough; albumin positive from stasis; death one month later; myocardial failure.
21	J. B.	54	190	90	100	111	Mitral regurgitation; dilatation arch aorta (?); sudden death three days later.
22	Miss J. L.	40	180	95	85	90	Paroxysmal tachycardia; heart block (?); systolic murmur apex; dyspnea.
23	Mrs.S.S.T.	71	240	105	135	128	Obesity; systolic murmur base and arch aorta; edema extremities; polyuria; syncopal attacks; pulse rate 32 to 36 for three months, due to heart block.
24	Mrs.D.A.C.	68	180	90	90	100	Complains of irregular heart action; palpitation and dyspnea on exertion; cardiac hypertrophy to left; systolic murmur upper aorta; accentuated second pulmonic; urine negative.

such cases and that in consequence blood pressure readings give one little clue as to the sequence of circulatory changes. To this I agree to the extent that an isolated reading of pressure in a patient during his last days of illness with vascular disease can be of little value. But readings at such times when compared with earlier readings taken before the break in compensation, would much more clearly explain the sequence of events leading to the gradual or rapid fall of systolic pressure as the myocardial force diminished. The systolic pressure frequently falls from 180 or 200 to 120 or below over a period of weeks or months as the myocardial force diminishes. With the low or normal diastolic pressures found in the cardiac group this would result in a heart-load ratio within normal limits (except in aortic regurgitation). If comparative readings had been made earlier in the disease it would have been found that the heart-load ratio like the systolic pressure was increased. This is shown in the following brief history of Case 3, Table 4:

Seven months before death the patient's systolic pressure was 180, diastolic 90, pulse pressure 90, heart load 100 per cent. As the myocardial force diminished, the systolic gradually fell to 125, diastolic 90, pulse pressure 35, and the heart load was 35 per cent. The ratio improved with compensation, so that after a few weeks the load was within normal limits, 58 per cent. Gradually decompensation occurred with tachycardia, absolute arrhythmia and acidosis. The systolic pressure was 100, diastolic 80, pulse pressure 20, and heart load 25 per cent. a few hours before death.

MYOCARDIAL AND VALVULAR LESIONS WITHOUT HYPERTENSION BUT WITH INCREASED HEART-LOAD PERCENTAGE

In this group there were 14 patients. The individual age was much lower than in the preceding groups. Excluding the 4 patients with aortic insufficiency, the systolic pressure averaged 112, the diastolic 60, and the pulse pressure 52. The heart-load ratio was 86 per cent., an increase above the normal of 36 per cent. The greatest increases in the heart-load percentage were in the four patients with aortic regurgitation, in which the average systolic pressure was 138, the diastolic 40, the pulse pressure 98, and the heart-load 245 per cent. In the consideration of heart-load, instances could be cited in which there existed a load of 100 per cent.; that is, an overload of 50 per cent., with few subjective symptoms of myocardial incompetency. Most of these patients were able so to regulate their lives that little cardiac strain occurred. It is merely to be emphasized that when the pulse pressure persistently equals the diastolic pressure with a resulting 50 per cent. *overload,* which means the expenditure of double the normal amount of kinetic energy on the part of the heart muscle, cardiac hypertrophy has occurred. The symptoms of cardiac incompetency may develop at any time of slight overstrain. Of course, the

presence of incompetent valves greatly adds to the myocardial embarrassment. This is especially true of aortic regurgitation, in which the load is greatly increased as mentioned above. This condition has long been recognized as one of the most serious of valvular lesions.

MYOCARDIAL AND VALVULAR LESIONS WITH DECREASED HEART-LOAD PERCENTAGE

In this group there were 10 patients, all of whom showed various degrees of cardiac dilatation or marked degrees of cardiac muscle weakness. In dilatation there is, as a rule, a more or less marked fall in the systolic pressure, pointing to the inability of the myocardium to furnish the requisite energy, while there is less change in the diastolic pressure. This produces a diminished pulse pressure until with marked incompetency there is little pressure in excess of that required to open the aortic valves; that is, the diastolic and systolic pressure tend to approximate each other. This is especially shown in Case 6 of Table 4. The average systolic pressure in this Group was 118, the diastolic 92, the pulse pressure 26 and the heart load 28 per cent. These cases show, I believe, such a marked reduction in the heart-load percentage because of myocardial fatigue or dilatation. The diminished heart-load corresponds to the "negative load" recently mentioned by Swan.[13]

This point has appeared to need emphasis, since it is a factor of importance not so much in the diagnosis of a marked degree of dilatation, as in those of lesser degree, in which, regardless of the skill of the physician in percussion, it is difficult, if not impossible, accurately to outline changes in the area of heart dulness.

CONCLUSIONS

From the study of these conditions, the following conclusions appear warranted:

1. The determination of systolic and diastolic pressures by the auscultatory method should supplant the palpatory method. The comparison of systolic, diastolic and pulse-pressures is of value in the clinical interpretation of circulatory changes and of more importance than the estimation of systolic pressure alone.

2. The pulse pressure measures the energy of the heart in systole in excess of the diastolic pressure. For clinical purposes it represents the load of the heart. Under normal conditions, it is approximately 50 per cent. of the diastolic pressure. The heart-load may therefore be expressed by the fraction,

$$\frac{\text{Pulse Pressure}}{\text{Diastolic Pressure}} \text{ or } \frac{\text{P.P.}}{\text{D.P.}}$$

13. Swan, J. M.: THE ARCHIVES INT. MED., 1915, xv, 269.

TABLE 3.—Myocardial and Valvular Lesions Without Hypertension but With Increased Heart Load Ratio

No.	Name	Age	S. P.	D. P.	P. P.	Cardiac Load Per Cent.	
1	C.McC.	11	130	50	80	160	Acute exacerbation of chronic endocarditis; double murmur in femoral and brachial; capillary pulse; aortic insufficiency.
2	Mrs.R.G.	25	138	35	103	300	Cyanosis with edema of limbs; extreme dyspnea; apex in left anterior axillary line; systolic and diastolic murmurs over all valve areas; capillary pulse; aortic insufficiency, 8/28/14.
..	.....	..	145	35	110	314	Ten hours before death, 8/30/14.
3	M. R.	69	125	58	67	115	Dyspnea; marked irregularity; rate 52; emphysema, chronic bronchitis; improved on caffein; myodegen. cordis.
4	Miss J.T.	25	128	72	56	77	Dyspnea and fatigue; mitral stenosis and insufficiency; marked irregularity; rate 56; irregularity increased under digitalis.
5	Mrs. W.W.	54	138	85	53	62	Fatigue on exertion and insomnia; systolic murmur over apex and loudest over aorta; transmitted to neck; slight dilatation of arch.
6	S. C.	13	90	55	35	63	Periodic syncopal attacks with bradycardia to 28-32; positive venous pulse; relative tricuspid insufficiency; heart block.

7	L. G. V.	54	90	50	40	80	Blurring vision; diarrhea and vertigo; luetic myocarditis and liver cirrhosis, one month before death.
8	H. L.	46	125	68	57	84	Partial syncope following undue exertion; left ventricle hypertrophy; "athletic heart."
9	P. M.	17	95	40	55	72	Acute infection undetermined origin; hemolytic anemia; red blood cells 952,000. Eventual recovery.
10	H. C.	18	110	60	55	83	Mitral regurgitation with apparent compensation.
11	R. S.	21	140	20	120	600	Aortic insufficiency and chronic endocarditis; diphtheroid bacillus recovered by blood culture; death five months later.
12	M. S.	34	140	60	80	133	Diastolic murmur over Erb's point; moderate grade aortic insufficiency with compensation.
13	Mrs. Dr. J.	68	125	58	67	115	Amebic dysentery in 1903; uncinariasis in 1910, never completely recovered; now severe secondary anemia, hemoglobin 20, red blood cells 2,290,000; stools contain *Amebae coli;* few distoma eggs; few hooklets of uncinaria; urine negative; systolic murmur over aorta transmitted to carotid; sclerosis of arch.
14	Miss J. C.	69	100	58	42	72	Periodic bleeding from right tuberculous kidney for seven years; secondary anemia; hemoglobin 25 per cent.; reds 2,500,000; systolic blow over apex and base. Five months before death.

TABLE 4.—Myocardial and Valvular Lesions With Decreased Heart Load Ratio

No.	Name	Age	S. P.	D. P.	P. P.	Cardiac Load Per Cent.	
1	Mrs.L.E.C.	64	170	130	40	30	Same as Case 17, Table 1; syncopal attacks; angina; suffocation; cardiac cough, systolic murmur at apex, left ventricle hypertrophy; dilatation, arrhythmia, 12/27/13. Death from angina, 10/13/14.
2	Miss M. S.	27	108	82	26	31	Enormous cardiac hypertrophy with dilatation, thrill over apex with systolic murmur, absolute arrhythmia, rate 164, positive venous and liver pulse. Death three months later.
3	Mrs. E. H.	73	125	90	35	35	Systolic blow at apex; perpetual arrhythmia; cardiac dilatation; edema of limbs; swollen liver, 7/15/14.
..	.....	73	150	95	55	58	Disappearance of edema with compensation, 9/3/14.
4	F. W. C.	77	100	75	25	33	Hydropericardium; hydrothorax; alcoholic cirrhosis of liver; cardiac dilatation; death one week later.
5	Mrs. J. C. M c F.	54	140	105	35	33	Dyspnea on exertion and weakness; heart dull tones over all; displacement of apex to left; dilatation.
6	K. M.	12	98	88	10	11.5	Congenital heart lesion; probably patent ductus arteriosus, hypertrophy and dilatation, three days before death.
7	Mrs. F.W.	27	125	100	25	25	Mitral regurgitation; perpetual arrhythmia; pulsus alternans; cardiac dilatation; in bed six months; general anasarca, 1/12/15
..	.....	27	125	105	20	19	Positive venous pulse neck, 2/20/15. Death five months later.
8	Miss M. W.	38	90	75	15	20	Old healed fibroid phthisis; myasthenia gravis; in bed twelve months.
9	C. McC.	48	105	95	10	10	End of third week typhoid; temperature normal; marked periodic delirium with exhaustion; eventual recovery.
10	Miss J. G.	40	80	65	15	23	Septicopyemia; multiple septic thrombi (staph. aureus); pulse 170 two hours before death.

3. Since the diastolic pressure represents the constant pressure between systoles, it is a better index of peripheral resistance and of hypertension than the systolic pressure. A sustained diastolic pressure of 105 to 110 or above signifies hypertension, irrespective of the height of the systolic pressure. The diastolic is less influenced by physiologic factors than the systolic pressure.

4. In arterial hypertension incident to myocardial and valvular lesions, the pulse pressure and heart-load are increased as a rule, the overload factor averaging 46 per cent. in the twenty-four patients of the cardiac hypertension group. In this group the diastolic pressure was persistently lower than in the cerebral hypertension group while the pulse pressure was increased. This produced an increased ratio between these two pressures, representing the expenditure of increased energy on the part of the myocardium in an attempt at compensation, with a consequent increase in the heart-load percentage. The greater the overload factor the greater is the apparent subsequent danger of myocardial exhaustion, dilatation, and its sequelae.

5. In the cerebral hypertension group the diastolic pressure is persistently high, from 120 to 160. This group comprises the nephritic cases, so-called, with symptoms of polyuria, albumin, casts and edema. The pulse pressure is not so greatly increased, as a rule, and the heart-load percentage is within normal limits of 40 to 60 per cent. The term cardiorenal disease applied to patients with cardiac manifestations in nephritis is a misnomer. Cardiac symptoms are many times present in such cases but the manifestations and terminal events of vascular disease associated with disturbed renal function are more cerebral than cardiac. If any compound name is applied descriptive of the condition, the term cerebrorenal would be more approximate. The term Vascular Disease, however, covers the ground more completely.

6. In acute circulatory failure due to shock, including hemorrhage, in an individual with a strong acting heart, the diastolic pressure is decreased, while the pulse pressure is increased, since the heart is exerting all its force in an endeavor adequately to supply the periphery with blood. This endeavor is a compensatory effort, since the arteries may be more or less emptied in shock. The rapid pulse rate and increased respirations are likewise compensatory efforts. When the heart muscle has eventually exhausted itself, the systolic pressure falls, which results in a lessened pulse pressure until there is little leeway between the diastolic and systolic pressures. The heart at this point fails to move sufficient blood to the periphery to supply the respiratory and cardiac centers and its work ceases.

7. In circulatory failure due to cardiac dilatation or myocardial degeneration incident to acute or long continued illness, the systolic

pressure falls and tends to approximate the diastolic pressure, with the result that the pulse pressure is decreased. The sequelae above mentioned soon appear and death occurs from insufficient blood supply to the respiratory and cardiac centers.

8. In acute infections a sustained pulse pressure warrants a more favorable prognosis, as a rule, than a low pulse pressure, other things being equal, although the change from normal to low pulse pressure in circulatory failure may occur very rapidly. As a rule, the lower the pulse pressure, the greater the danger of circulatory failure.

9. Measures directed to the reduction of blood pressure by diet, habits, venesection and vasodilators are usually indicated in the cerebral hypertension group because of the high diastolic pressure, but are rarely indicated in the cardiac hypertension group. The high systolic pressures in the cardiac hypertension group are compensatory measures and rest; digitalis, strophanthin, camphor or caffein are indicated when the heart muscle shows signs of fatigue.

THE TREATMENT OF CARDIAC INSUFFICIENCY BY A NEW METHOD OF EXERCISE WITH DUMB-BELLS AND BARS

THE CIRCULATORY REACTION TO EXERCISE AS A TEST OF THE HEART'S FUNCTIONAL CAPACITY *

THEODORE B. BARRINGER, JR., M.D., AND JACOB TESCHNER, M.D.
NEW YORK

Brilliant as has been the advance in our knowledge of the pathology and diagnosis of cardiac disease during the last decade, therapeutics in this field are practically the same as they were twenty years ago, and consist chiefly in rest, diet, and digitalis.

The possibility of developing the inherent power of the heart muscle was affirmed many years ago by Oertel, who used the very arduous exercise of hill climbing for this purpose. Since then the Nauheim school has been the chief exponent of the treatment of cardiac insufficiency by exercise and baths. The literature on these methods is meager, and judging from the scarcity of published reports, but few physicians in this country have been enough impressed with their value to give them a trial. Possible reasons for this are the elaborate outfit required for certain of them, lack of knowledge of the various special exercises, and more than anything else, perhaps, our inability to form an accurate estimate of the patient's cardiac efficiency. No method of increasing the strength of the heart muscle can be carried out in any but the most empiric way, nor can the results be correctly appraised if we do not first possess a fairly reliable test for determining the heart's functional capacity.

Before treating patients with cardiac insufficiency by the new method of exercise referred to in our title, it seemed essential, therefore, to investigate the various tests for cardiac efficiency which have been proposed, although the validity of each has been questioned and no one has met with general acceptance.

In 1905, Gräupner originated a test consisting in deductions made from frequent observations of the pulse and systolic blood pressures after measured amounts of work, performed by means of an ergometer (that is, a form of stationary bicycle). His plan seemed peculiarly well adapted to our ends, for the exercises we used were of a kind

* Submitted for publication June 3, 1915.
* From the Medical Service of The House of Relief.
* Read before the New York Academy of Medicine, May 13, 1915.

that permitted a fairly accurate estimation of the amount of work performed. So we carried out Gräupner's test in 150 experiments on fifteen normal people, using our exercises instead of the ergometer.

EXPERIMENTS ON NORMAL PEOPLE

The pulse rate, systolic and diastolic pressures[1] were first taken. Then a measured amount of work was performed and the pulse rate and blood pressures were taken immediately after the cessation of work, and every one or two minutes thereafter, by the same observer. Then the same procedure was repeated with an increased amount of work.

Charts 1 and 2 show the type of reaction we invariably found. Directly after a moderate amount of work, the systolic blood pressure was raised and the pulse accelerated, both then rapidly falling to and below the figures noted before the work began. The rise was proportional to the amount of work, the time in which it was performed and to the individual's physique and muscular training. As soon as the work exceeded a certain amount, which varied for different individuals, we regularly found that the systolic blood pressure did not reach its highest point immediately after work, but a minute or so later at a time when the pulse rate had dropped back toward normal. The amount of work sufficient to produce this delay in the systolic blood pressure's reaching its maximum was generally accompanied by hyperpnea (in one person by vertigo and nausea), and the subject of the experiment was conscious that he had done a hard bit of work, sometimes unpleasantly so.

The physiologic explanation of this phenomena is still obscure. We know that during exercise the pressure in the aorta mounts rapidly, making the emptying of the left ventricle increasingly difficult. The exercise continuing, the pressure falls slowly, thereby relieving the strain on the ventricle. Just what part dilatation of the skin vessels or the splanchnic area plays in causing this fall we no not know, but it is evidently a defensive reaction to prevent the left ventricle from becoming insufficient.

Gräupner[2] measured the blood pressure at frequent intervals in patients with cardiac insufficiency during and after increasing quantities of work, and showed that when the work reached a certain amount the pressure fell slowly, and, the work stopping, there ensued the delayed rise we have observed. He noted also that the harder the work, the more marked the subsequent delay, until, finally, in heavy

2. Gräupner: Deutsch. med. Wchnschr., 1906, No. 26, p. 1028.

1. After making numerous measurements of the diastolic pressure we found them of no value for our purpose and so omitted them.

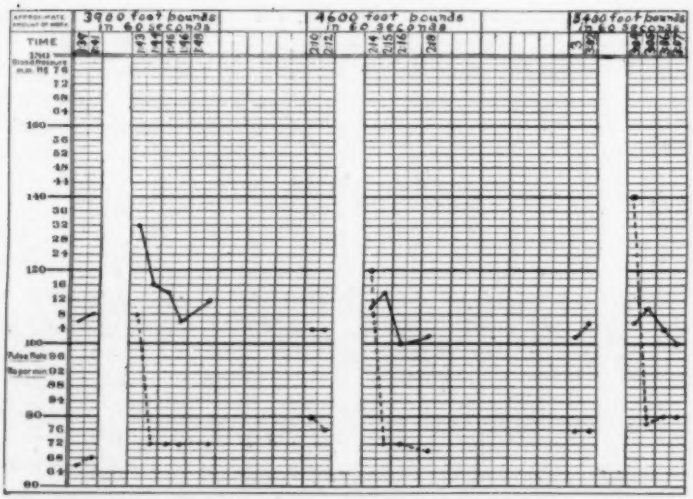

3960 foot pounds in 60 seconds
4600 foot pounds in 60 seconds
5460 foot pounds in 60 seconds
TIME
Blood Pressure m.m. Hg
Pulse Rate Beats per min.

Chart 1.—Type of reaction in normal persons after measured amount of work.

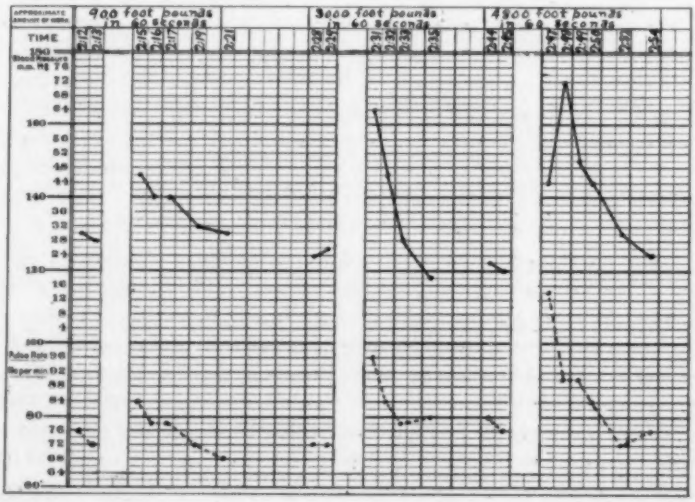

900 foot pounds in 60 seconds
3000 foot pounds in 60 seconds
4800 foot pounds in 60 seconds
TIME
Blood Pressure m.m. Hg
Pulse Rate Beats per min.

Chart 2.—Reaction noted in normal persons after moderate amount of work.

work the pressure immediately after was lower than before, and slowly returned to and above the original level.

The exercise incident to an active physical life must frequently produce this delayed rise and the fact that damage is rarely done to the heart shows the efficiency of this protective mechanism. We found that one week's training of a normal person would increase markedly the quantity of work he could do before a delayed reaction was produced.

TEST FOR ESTIMATING THE HEART'S FUNCTIONAL CAPACITY

As a result of our experiments on normal people we were inclined to believe that in certain deductions made from the pulse and blood-

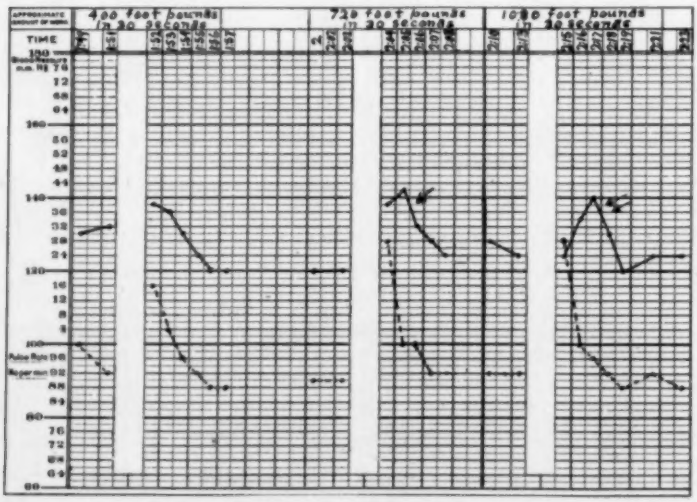


Chart 3.—Effect of overtaxing left ventricle.

pressure reactions to a measured amount of work, we possessed a valid test of the heart's functional capacity, even though we had no proved physiologic basis for this assumption. As soon as the quantity of work was sufficient to produce a delayed reaction, we considered that we had overtaxed the heart's reserve force at that particular time and secured a measure of its efficiency. As shown in Chart 1, if 3,900 foot-pounds of work performed in 60 seconds is followed by a rapid fall in blood pressure, and 4,600 foot-pounds of work in 60 seconds is followed by a delayed reaction, the functional capacity of that heart may be expressed as an ability to supply the amount of blood to the muscles necessary for doing between 3,900 and 4,600 foot-pounds of work in 60 seconds.

The validity of this test of the heart's functional capacity unexpectedly received confirmation during the study of five patients suffering from angina pectoris. While estimating their cardiac efficiency we found in four of them that just as soon as work sufficient to cause a delayed rise in blood-pressure was given, a slight anginal attack was produced. After resting some minutes each patient was then given work increased by several hundred foot-pounds. A more marked delay in the blood-pressure rise and a more marked anginal attack was produced. In other words the overtaxing of the left ventricle was evidenced clinically not only by the blood-pressure reaction but almost simultaneously by the angina. Chart 3 depicts this incident in one of the angina cases.

Accordingly we adopted this method of frequent pulse and blood-pressure determinations following a measured amount of work, as a guiding principle in the treatment of cardiac insufficiency, and it has worked out so well that we feel the validity of this criterion of the heart's efficiency has been practically established.

The pulse and blood-pressure curves we obtained after measured amounts of work differ in several very important points from Gräupner's results and these differences do much to invalidate Gräupner's conception of the essentials of his test. Our conclusions as to the import of the pulse and blood-pressure curves are naturally quite different from his, so different that our test cannot properly be called the Gräupner test. In a later article we shall discuss this matter at greater length.

METHOD OF EXERCISE

The new method of exercise which we have been trying out this past year is new only in its application to cardiac insufficiency. It was devised many years ago by the senior author, Dr. Teschner, and has been used by him constantly in the practice of orthopedics. Several of his patients were suffering also from chronic valvular disease with cardiac insufficiency and he noted a marked improvement in their circulatory symptoms, attributable apparently to these exercises, so we were encouraged to experiment with them on a series of patients suffering from various cardiac disorders.

The apparatus used consisted of dumb-bells weighing from 3 to 25 pounds each and steel bars varying from 10 pounds upward in weight, with which different movements of flexion and extension were carried out. It was possible to measure the approximate number of foot-pounds of work performed in each exercise.

In treating our patients we followed this routine; 50 or 100 food-pounds of work was given with a pair of 5 pound bells by pushing them alternately above the head. The pulse and blood pressure were

taken before and every minute after the exercises. If they showed a normal type of reaction, in a few minutes another piece of work was given, increased by 50 or 100 foot-pounds through using heavier bells. Sooner or later, we reached an amount of work which was followed by a delayed rise in blood pressure and we knew that the functional capacity of the patient's heart had then been exceeded. We found that many of our patients showed a cardiac efficiency of only a few hundred foot-pounds, which contrasted strikingly with the efficiency of a normal heart, which may measure as much as 7,000 foot-pounds performed in two minutes.

The daily exercise of our patients was arranged as follows: Having found in a given patient that 800 foot-pounds produced a delayed rise, his future work was limited to 700 foot-pounds for a period of seven days. Each day he was given this 700 foot-pounds to do from four to six times, with five or ten minutes rest in between, so that about an hour was used for the exercise period. At the end of seven days the heart's functional capacity was again tested and, if it had increased, the work for the next week was kept just below the amount that produced a delayed reaction.

As the patient's heart increased its efficiency, and the increase was often surprisingly rapid, various other exercises were added to the initial one of pushing dumb-bells above the head, exercises which utilized the trunk muscles and enabled us to increase markedly the number of foot-pounds performed without tiring excessively any one group of muscles. These were the swing, in which a bell is swung from the floor above the head and down again, the elbow and wrist being fixed, and bar work in which a steel bar is pushed above the head, the patient standing, or lying on the back. Each movement was repeated from 10 to 20 times, the patient being carefully instructed not to hold his breath while exercising on account of the pressor effect of a closed glottis. The time consumed in each form of exercise varied between 30 and 120 seconds. Patients were frequently conscious of improvement after six treatments. We usually gave them from twenty to thirty treatments. Sometimes we were in doubt as to whether a delayed reaction had occurred, generally in patients with fibrillating hearts. A repetition of the exercise with a slight increase of work would always clear this up. Sometimes the pressure after work was found to be lower than before. This is to be regarded as an extreme type of delayed reaction and means that the heart has been decidedly overtaxed by the preceding work. The production of one or two delayed reactions in a patient with cardiac insufficiency never seemed to have any harmful result.

The time required for the pulse rate and blood pressure of a delayed reaction to return to the previous level was a distinct aid in estimating the condition of the heart muscle. In one of our patients, who subsequently died with double mitral, double tricuspid and double aortic lesions, and a cardiac efficiency of but 200 foot-pounds in thirty seconds, ten to twenty minutes would almost always elapse before the return to normal of a delayed reaction.

PATIENTS SELECTED FOR TREATMENT

We selected for treatment ambulatory patients with chronic valvular or myocardial disease and varying stages of decompensation. Any suggestion of an acute process, any history of recent emboli or a persistently high blood pressure was considered to be a contraindication for the exercise treatment. Many of the patients had entered the hospital suffering from an acute insufficiency and had had the usual treatment of rest, diet, and digitalis. As soon as they were able to be up and walk around, they were given the exercises.

PATIENTS WITH MITRAL LESIONS

Table 1 summarizes our results in six of these patients. Three patients whose histories follow showed marked improvement.

TABLE 1.—SUMMARY OF RESULTS IN SIX PATIENTS WITH MITRAL DISEASE

No. and Name	Age	Initial Cardiac Capacity foot-pounds	Final Cardiac Capacity foot-pounds	Initial Lung Capacity cu. in.	Final Lung Capacity cu. in.
1 T.	40	150	520	70	96
2 F. D.	53	150	600	70	110
3 J. T.	28	?	?	162	180
4 B.	31	75*	...	...	...
5 P.	55	120	280	50	62
6 D.	24	100-200	525	?	?

* Exercise discontinued after five lessons.

Three patients whose histories follow showed marked improvement.

CASE 1.—M. T. (Patient 1), a woman, aged 40, had been sick intermittently for a year, suffering from dyspnea and swelling of the feet and abdomen. On her second admission to the hospital she was cyanosed and orthopneic, her legs were much swollen, the liver extended six inches below the costal margin, there was free fluid in the abdomen and a small amount in each pleural cavity. Her heart showed a double mitral lesion and auricular fibrillation. After being treated with digitalis she was able in a few weeks to get around the ward. Several weeks later the exercise course was begun and she received fifty-eight treatments.

Twice the exercises were suspended and she was given digitalis (12 drams of the tincture altogether). After these two interruptions she improved steadily.

The edema of the legs subsided, the swelling of the liver lessened, and her strength returned. Her cardiac efficiency increased from 150 foot-pounds to 520 foot-pounds, and her respiratory capacity from 70 cubic inches to 96 cubic inches. Today (four months after stopping the exercises) she is doing her housework and feels "better than she has for years."

CASE 2.—F. D. (Patient 2), a laborer, aged 53, had suffered from dyspnea and swelling of the ankles for a month before admission. On entering the hospital he was cyanosed and orthopneic. There was pretibial edema, fluid in the right pleural cavity and the liver was enlarged. His heart showed a mitral regurgitation and auricular fibrillation. Twenty-five ounces of clear fluid was taken from the right chest, and he received altogether, 9 drams of tincture of digitalis. Seven weeks later his exercise was begun. He had twenty-six treatments and improved markedly. His cardiac efficiency increased from 150 foot-pounds to 600 foot-pounds, and his lung capacity from 70 to 110 cubic inches. He went to work immediately after discharge, and did light work steadily for six weeks and then his dyspnea and swelling of the ankles returned. His breakdown was due to his shoveling snow for six hours one night after working all day. He recovered after three weeks stay in the hospital and began work again.

CASE 3.—J. T. (Patient 3), a barber, aged 28, had a history of dyspnea, swelling of the ankles and occasional pulmonary infarction extending over three years. He had a double mitral lesion and auricular fibrillation. He improved markedly in the exercises and remained well for three months. Then he had another pulmonary infarct and decompensation followed.

Three patients did not do well. In one the treatment had hardly started (but five lessons were given) when we had to stop. Another improved slowly and then retrograded. This latter patient left the hospital against advice two weeks after treatment was discontinued, but returned in ten days and died twelve hours later. The necropsy showed an enormous heart with double mitral, double tricuspid and double aortic lesions. A third patient, a woman aged 55, with chronic bronchitis, a double mitral lesion, auricular fibrillation, and rather high blood pressure, improved slightly and then retrograded. She suffers now, two months after her last treatment, from recurring hydrothorax, shortness of breath and pretibial edema.

TABLE 2.—SUMMARY OF RESULTS IN PATIENTS WITH MYOCARDITIS

No. and Name	Age	Initial Cardiac Capacity foot-pounds	Final Cardiac Capacity foot-pounds	Initial Lung Capacity cu. in	Final Lung Capacity cu. in.
1 P. R.	39	700	3,000	215	278
2 K.	64	3,000 1,400 400	4,800	172	178
3 O. B.	54	800	1,600	?	?
4 D.	56	?	?	...	...

PATIENTS WITH MYOCARDITIS

CASE 4.—P. R. (Patient 1, Table 2). This was a most interesting case in a laborer, aged 39, with splendid muscular development, who contracted bronchitis on Oct. 17, 1914. For two weeks he complained of cough, weakness and shortness of breath. On Oct. 29 he lifted one end of a cask weighing 1,200 pounds. He was immediately conscious of palpitation, and on trying to work again became very short of breath. He was helped to his home and the next day was admitted to the hospital. He was orthopneic, markedly cyanosed, and his ankles were swollen. His heart was rapid, regular, and showed at the apex

a gallop rhythm and systolic murmur. The lungs were clear. He was given 0.0005 of strophanthin intramuscularly and later received digitalis, 5 drams of the tincture, altogether. On November 5 he was up in a chair and the digitalis was stopped. Four days later his exercises were begun. He received thirty-four altogether, and improved remarkably, his cardiac capacity increasing from 700 foot-pounds in forty-five seconds to 3,000 foot-pounds in seventy-five seconds. Today he is doing light work and feels well.

Chart 4 represents his electrocardiograms, the first taken November 7, two days after stopping digitalis. His exercises were begun on November 9 and on December 3 the second electrocardiograms were taken. On November 7, T_1 and T_2 were directed downward. On December 3, T_1 and T_2 were directed upward. Also P was much higher on December 3 than on November 7. The initial reversal of T_1 and T_2 may have been, as A. E. Cohn has pointed out, a digitalis effect, or it may have indicated, as Einthoven holds, a damaged heart muscle. The change in the T waves following the exercises and the marked

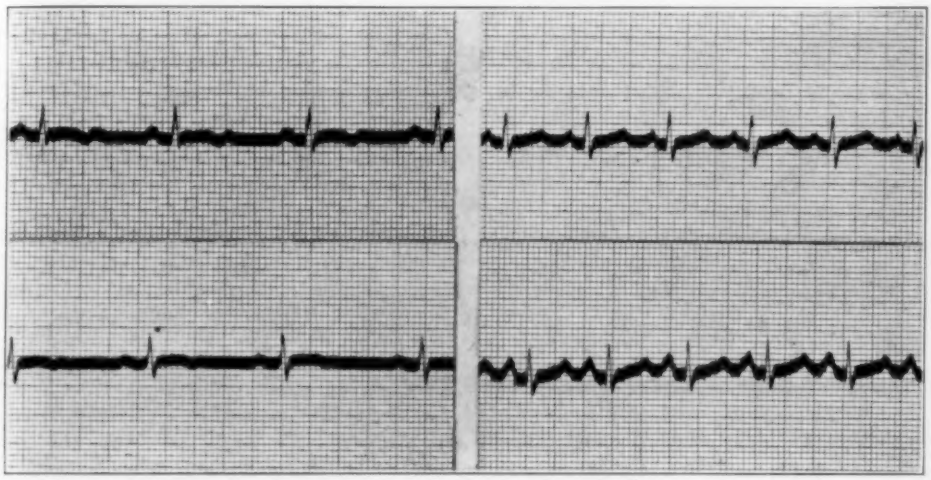


Chart 4.—Electrocardiogram of Patient P. R.. Leads 1 and 2 (at left) taken Nov. 7, 1914, two days after stopping digitalis. Leads 1 and 2 (at right) taken Dec. 3, 1914.

clinical improvement may have been due either to the exercises or to the release of the heart from digitalis influence. In regard to the significance of the increase in the height of P, it may be said that cases of compensated mitral stenosis generally show a large P wave.

Case 5.—K. (Patient 2, Table 2), was a business man, aged 64, who had no symptoms referable to his heart, but complained of occasional attacks of vertigo, acompanied by increased blood pressure. His electrocardiograms showed some heart muscle involvement, chiefly left ventricle hypertrophy. He was given a course of twenty-one exercises to see if we could influence the form of the cardiogram. The estimation of his cardiac efficiency showed a peculiar result. The first day it was 3,000 foot-pounds in sixty seconds. Two days later it was 1,400 foot-pounds in sixty seconds, and two days still later it was but 400 foot-pounds in thirty seconds. He felt perfectly well and we could not explain this surprising decrease. From that time on by carefully grading his exercise, his cardiac efficiency increased steadily until it reached 4,800 foot-pounds in sixty seconds. His electrocardiograms showed no changes.

CASE 6.—O. B. (Patient 3, Table 2), was a retired business man, aged 54, suffering from angina pectoris. He complained of shortness of breath and slight anginal attacks generally caused by walking or mental excitement. He was overweight; examination of his heart was negative and his Wassermann test was negative. His cardiac efficiency increased from 800 foot-pounds to 1,600 foot-pounds, but his angina was not improved. His electrocardiogram showed slight changes.

CASE 7.—D. (Patient 4, Table 2), was a woman, aged 56, suffering from dyspnea on exertion. She was obese, weighing 218 pounds. Her heart showed an auricular fibrillation but no murmurs. Her blood pressure ranged between 180 and 210 mm. Hg. The urine was negative. She showed no improvement after twenty-eight exercises.

PATIENTS WITH AORTIC REGURGITATION

We treated three patients with this lesion, all young men under 25 with high initial cardiac capacities and with no evidence of insufficiency except shortness of breath on exertion. They improved much

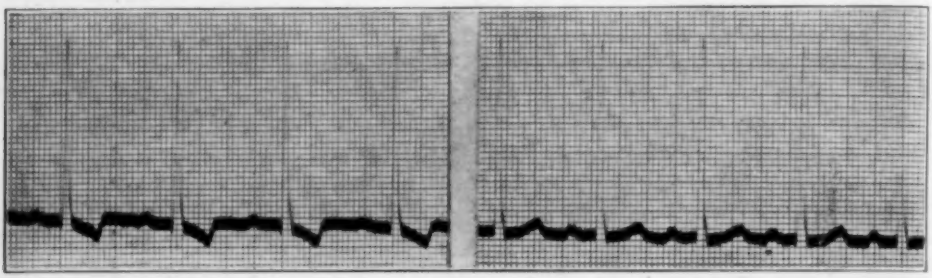


Chart 5.—Electrocardiogram in case of aortic regurgitation. Lead 1 (at left) taken before the exercise course. Lead 2 (at right) after exercise course.

more quickly than did the patients with mitral disease, feeling decidedly better after four or five treatments. Their youth, the slight degree of decompensation, and the intenser effect of exercise on the left ventricle, explain the rapidity of their improvement.

Chart 5 shows the electrocardiograms of one if these patients, taken before and after the exercise course. He had received no digitalis for months before the first electrocardiogram. It shows an inverted T_2 wave which becomes erect in the second one, at which time he showed a marked clinical improvement. R_2 and R_3 were taller in the first, than in the second electrocardiogram.

Chart 6, represents the electrocardiograms of another aortic patient taken before and after eleven treatments with exercise. They show a marked increase in the height of R_1 and an increase in the negativity of R_2. The average height of R_1 in the first was 10 mm., in the second 25 mm. R_2 in the first measured —6 mm., in the second, —15.

The electrocardiograms of a third patient showed an increase of R_2 from 18 mm. to 27 mm., and of R_3 from 8 mm. to 16 mm.

These last two patients showed an increase in the height of the R waves accompanying clinical improvement, while Patient 1 showed a decrease in the height of his R waves.

We took electrocardiograms of all our patients before and after the exercise treatment, and the four described are the only ones showing decided changes. But one patient showed changes pointing to an increased left ventricular hypertrophy.

SUMMARY OF HEART CASES

Nine of the thirteen patients treated showed marked improvement attributable apparently to the exercises, for with one exception, no other treatment was given during the exercise course. Three of the

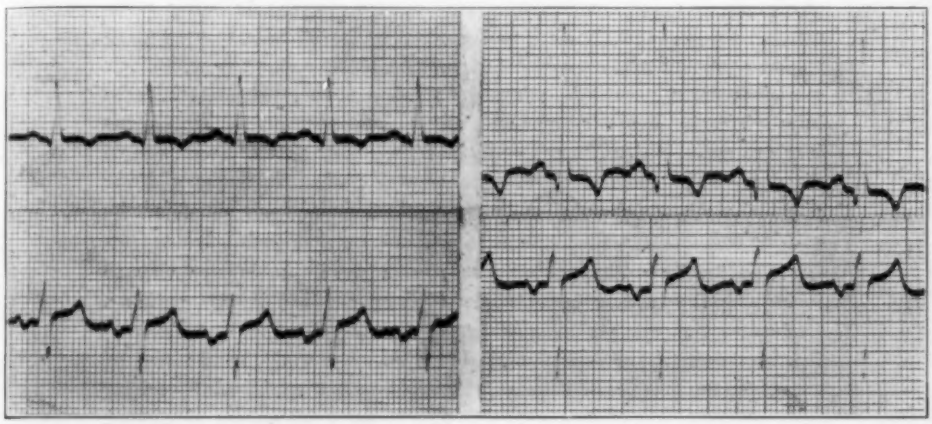


Chart 6.—Electrocardiogram in case of aortic regurgitation (at left) before exercise, and (at right) after exercise.

patients, who did not improve suffered from mitral disease with marked decompensation and showed very low initial cardiac and respiratory capacities.

PHYSIOLOGY OF EXERCISE

The marked increase in the heart rate and raising of the systemic blood pressure caused by exercise in general are undoubtedly the chief physiologic factors in producing the many beneficial effects of muscular activity. Increased ventilation of the lungs also plays an important rôle.

In our system of exercises the pulse rate is increased and the blood pressure raised for very brief periods of time. The respiration is quickened likewise for a few seconds. Whether this transient excitation of the circulatory system repeated six or seven times in the course

of an hour would have any appreciable general effect on a normal person was a question which suggested itself when making our earlier experiments to secure a valid test of the cardiac efficiency. Accordingly we gave the exercises to six normal people for a month, using heavier weights, and found to our surprise that the benefit to their health (appetite, digestion, sleeping and general efficiency), was marked and unmistakable. The improvement in the heart patients must have been due to the same physiologic cause. To be more specific, the raising of pressure in the aorta improves the coronary circulation and peripherally it causes a more rapid blood flow through each organ. Also the help to the venous circulation afforded by alternate relaxation and contraction of the muscles is considerable. The lymphatic flow in particular is aided by this muscular action, thereby bringing more quickly the end-products of metabolism to the blood stream and so to the excretory organs. Also the increase in lung capacity which our exercises seem peculiarly adapted to bring about, aid materially in improving the heart action and the pulmonary circulation. This increase amounted to 36 per cent. in four of our patients with mitral disease. The psychical effect on a cardiac patient of actually doing physical work and feeling better rather than worse for it, must not be overlooked.

It is hardly probable that our results were due in any way to increasing the cardiac hypertrophy already existing in our patients. Failure to demonstrate any changes in the electrocardiograms indicating increased hypertrophy with one exception, and the absence of change in the physical signs, and the fact that the actual total working time of each patient was not over five to eight hours for the entire course, all militate against such a supposition.

COMPARISON OF OUR EXERCISES WITH RESISTANCE GYMNASTICS

Resistance gymnastics is the chief form of exercise used today in cardiac insufficiency and forms an important part of the Nauheim treatment. A comparison with our system of exercises might be of interest.

The most striking feature of the exercises we advocate is their concentration. Each series of movements lasts from thirty to one hundred and twenty seconds and is followed by a rest from five to ten minutes. It would be quite possible to spread the work over from ten to fifteen minutes so that the patient would accomplish the same number of foot-pounds in the longer period of time. This we have done but found there was a much slighter effect on the pulse and blood pressure. If the rise in blood pressure and increase in heart rate are the essen-

tial physiologic causes of the benefit derived from exercise, then our present concentrated form of exercise must be far more efficient than any other, *provided always* that we can guard against too high a blood pressure and too rapid a pulse. We feel convinced that our test, the validity of which we took such pains to establish, protects us against such danger.

On reading the description of resistance gymnastics in the last edition of Schott's "Treatment of Chronic Diseases of the Heart," one is impressed with the extreme gentleness of the exercise, and the impossibility of measuring the work performed, slight though it is. On page 253, there is a chart showing the effect of the exercises on a low blood pressure. The systolic pressure taken before exercise by palpation is 115 mm. and pulse 82. Taken after 25 minutes of exercise the pressure is 120 (by palpation) and the pulse 72. It is needless to say that a variation of 5 mm. in the systolic pressure is trivial and will be found in any normal person who is sitting quietly in a chair. Also the margin of error in taking blood pressure by palpation frequently amounts to more than 5 mm. On page 55, a chart is reproduced showing that the same exercises *reduce* high blood pressure. Before exercise the systolic blood pressure was 175 and pulse 81; after thirty minutes of exercise the pressure was 160 mm. and pulse 62. If readings are made every five minutes on a patient with hypertension, sitting quietly in a chair, they will be found to vary as much as 10 mm. If a patient talks they will vary much more.

We have given our exercises cautiously to ten patients with high blood pressures and found that invariably a very small amount of work caused a *rise* of pressure which was followed by a fall to and below the preexercise figure.

That any form of exercise can raise a low pressure and lower a high pressure, the readings being taken at synchronous periods during or after exercise, is physiologically incomprehensible.

The only reasonable explanation of the charts just described is that they represent normal variations in blood pressure and would have been found whether or not the resistance exercises were carried out.

The good results unquestionably obtained at Nauheim, must be caused by the effervescing baths, for charts published in the above-mentioned work show a more marked pressor effect from the baths than from the resistance gymnastics.

CONCLUSIONS

1. The validity of the postexercise blood-pressure test of the heart's functional capacity has been established.

2. Although our experience is limited to a small group of patients, we feel that our system of exercise affords a valuable adjunct to the means already at our disposal for treating cardiac insufficiency.

We are much indebted to Dr. H. B. Williams for doing the electrocardiographic work. We wish also to express our appreciation of the very material help rendered by Dr. H. S. Valentine and Dr. F. W. Fiedler in carrying out the work recorded above.

34 West Eighty-Fourth Street.

THE RESISTANCE OF THE RED BLOOD CELLS TO HYPOTONIC SALT SOLUTION IN THE VARIOUS ANEMIAS

WITH OBSERVATIONS ON THE RESISTANCE AFTER ARSENICAL TREATMENT, AND AFTER SPLENECTOMY *

LEWIS WEBB HILL, M.D.
BOSTON

The resistance of the red blood cells has been extensively studied in the last few years, in various connections. There seems to be a considerable discrepancy in the results of the various investigators as to whether or not the resistance to hypotonic salt solution is raised or lowered in primary and secondary anemias. The purpose of this paper is to report a somewhat larger series of cases with anemia than has before been studied, as it is felt that the discrepancies in the results of various investigators may have been due to the fact that not enough cases were studied.

There are different ways of studying the resistance of the red cells. The methods used have been three:

1. The physicochemical method, with hypotonic salt solution.
2. The chemical method, with saponin or allied substances.
3. The biological method, with specific hemolysins.

It cannot be said that any one of these methods parallels the destruction of red blood cells in the body in cases of anemia. We know that such destruction is probably brought about by toxic substances, the exact chemical nature of which we do not know.

Bigland[1] says, "the popular physico-chemical procedure of hemolysis by means of hypotonic salt solution has a great objection—its artificiality. If it is wished to examine a patient's blood with regard to its resisting powers against the pneumococcus, is it any advantage to inject tubercle bacilli, and then draw conclusions from the results?"

With this we agree, and believe that the same applies to saponin, or to any specific serum, when used as a hemolytic agent. Hemolysis with saponin, with hypotonic salt solution, and with specific serums are probably three entirely different processes, and what holds for the one does not hold for the other, as has been shown many times.

---

* Submitted for publication July 1, 1915.

* From the West Medical Service, Massachusetts General Hospital. Dr. Richard C. Cabot, Chief of Service, Dr. Roger I. Lee and Dr. William H. Smith, Visiting Physicians.

1. Bigland: Quart. Jour. Med., Oxford, 1914, vii, No. 28, p. 369.

I do not intend to discuss hemolysis by saponin or specific serums at all, but to confine myself to experiments with hypotonic salt solution, bearing in mind that conclusions drawn from this form of hemolysis cannot be applied to the other two forms, nor directly to any phase of disease. In previous work, in general, investigators have used widely different methods, and this partly accounts for the variation of results.

The several factors concerned in the accuracy of the results are:

1. The method of making up the dilutions of salt solution, whether accurately measured in burets, or by the "drop" method.

2. The state in which the blood is examined, whether as washed cells or as whole blood.

3. The proportion of blood cells to salt solution in each tube.

4. The method of reading hemolysis.

These discrepancies make it somewhat difficult to compare results. In 1902 Veyrassat[2] studied the resistance of the red cells in pernicious and secondary anemia, and found that in pernicious anemia it was decreased, but increased in secondary anemias.

In 1903, Ribierre,[3] studying normal blood, found that initial hemolysis was at 0.44 per cent. salt solution, complete hemolysis at 0.34 per cent. In 1907 Chauffard[4] wrote his classical article on chronic family jaundice, in which he brought forward the fact that there was an increased fragility of the red cells in this disease. Everyone who has studied chronic family jaundice since has confirmed this observation. In the same year Chauffard and Rendu[5] studied a series of 10 normal cases, and found that hemolysis began at 0.46 and was complete at 0.38. Paoloni[6] found that there was always a diminution of resistance in anemia, whether primary or secondary. In normal blood, he found that hemolysis began at 0.44 and was complete at 0.36.

Ehni and Alexieff[7] reported two cases of pernicious anemia with decreased resistance.

Weill and Dufourt[8] believe that in the presence of any plasma harmful for them the red blood cells develop an increased resistance.

Jakuschewsky,[9] coinciding with Weill and Dufourt, believes that there is increased resistance as long as toxic substances are circulating

2. Veyrassat: Lyon méd., 1902, No. 25.
3. Ribierre: Thèse de Paris, 1903, p. 106.
4. Chauffard: Semaine méd., Paris, 1907, p. 25.
5. Chauffard and Rendu: Presse mèd., 1907, xv, 345.
6. Paoloni: Policlinico, Rome, 1913, No. 6, p. 243.
7. Ehni and Alexieff: Compt. rend Soc. de biol., 1908, lxiv, 1101.
8. Weill and Dufourt: Presse méd., xxi, No. 56, 565.
9. Jakuschewsky: Russ. med. Rundschau, 1904, No. 6, p. 345; Folia Hematol., ii, p. 21.

in the blood. Morawitz and Pratt[10] found that in experimental anemias produced with phenylhydrazinhydrochlorid, there was increased resistance.

Snapper[11] found that red blood cells obtained after severe hemorrhage were more resistant than those obtained beforehand, and that young cells were more resistant than older ones.

McNiell[12] studied saponin hemolysis, and found that some cells which had an increased resistance to hypotonic salt solution, had a decreased resistance to saponin. This was especially true of blood from cases of obstructive jaundice.

He also found that immersing the cells in hypertonic solution for a period of time increased their resistance. He found that in all cases in which there was a diminution in the number of red cells there was increased resistance to saponin, with the exception of pernicious anemia, which showed practically normal resistance.

Bigland,[1] in six cases of pernicious anemia, found that the resistance was either normal, or very slightly decreased. In secondary anemia he found a slightly increased resistance.

A criticism of all these results is that not enough cases were studied.

TECHNIC

The method used in the cases studied at the Massachusetts General Hospital was as follows:

About 6 c.c. of blood is withdrawn from the arm vein with a needle and glass syringe. This is transferred to a test tube half full of 0.5 per cent. sodium citrate solution in 0.9 per cent. sodium chlorid. The tube is then inverted two or three times to insure proper mixing. As soon as possible (certainly within three hours) the blood is centrifuged and the cells washed twice with 0.7 per cent. sodium chlorid. As much of the supernatant fluid as possible is drawn off with a pipet, and the remaining blood cells are used in the test, without further dilution. The hypotonic sodium chlorid solutions are made up from a 1 per cent. solution of chemically pure sodium chlorid and distilled water. The solutions run in strength from 0.70 per cent. to 0.175 per cent., and are kept in tightly corked 100 c.c. bottles.

Exactly 1 c.c. of each one of these solutions is drawn off in a pipet, and placed in a series of small test tubes; 0.05 c.c. of the blood cells is then run into each tube, from a small, accurately graded pipet, each tube is inverted twice and allowed to stand two hours at room temperature; at the end of this time the tubes are read. As initial hemolysis I have taken the point at which there is the first tinge of pink in the salt solution; as complete hemolysis the point at which there can no longer be seen any sediment of blood cells in the bottom of the tube. There is nothing difficult or complicated about this method; its only disadvantage is that is takes considerable time.

---

10. Morawitz and Pratt: München. med. Wchnschr., 1908, ii, No. 25.
11. Snapper: Biochem. Ztschr., 1912, xliii, 256.
12. McNiell: Jour. Path. and Bact., London, 1911, xv, 56.

NORMAL BLOOD

Nineteen normal bloods were examined and were found to have an average resistance of 0.457 for initial hemolysis, and 0.340 for complete. The figures for the most fragile normal blood were 0.475 (initial) and 0.375 (complete). The lowest point at which hemolysis began in any case was 0.425; the lowest point at which it was complete was 0.275. The lowest point at which hemolysis began in any case was 0.425; the lowest point at which it was complete was 0.275. The normal bloods seem to have a fairly constant resistance, the most constant figure being the point of initial hemolysis.

SECONDARY ANEMIA

Twenty-four cases of secondary anemia due to various causes, were examined. (See tables.)

In general, hemolysis in secondary anemia seems to start at a dilution somewhat less than it does in normal blood, and to extend over a larger number of tubes, so that the point of complete hemolysis is somewhat lower than in normal cases. In anemic bloods some of the cells seem less resistant than normal, some more resistant. The young cells have been thought to be the most resistant of all cells, but Pepper and Peet[13] were not able to demonstrate any increase in resistance of the so-called "skeined" or reticulated forms, seen especially in anemic bloods, and certainly in cases of chronic family jaundice, in which from 20 to 30 per cent. of the red cells are of this reticulated type,

TABLE 1.—NORMAL BLOODS

	Initial Hemolysis	Complete Hemolysis
1	0.475	0.375
2	0.450	0.325
3	0.475	0.350
4	0.475	0.350
5	0.475	0.325
6	0.425	0.275
7	0.425	0.325
8	0.450	0.325
9	0.475	0.300
10	0.450	0.300
11	0.450	0.350
12	0.450	0.350
13	0.450	0.350
14	0.475	0.350
15	0.475	0.300
16	0.425	0.325
17	0.475	0.375
18	0.450	0.350
19	0.450	0.375
Average	0.457	0.340

13. Pepper and Peet: The Resistance of Reticulated Erythrocytes, THE ARCHIVES INT. MED., 1913, xii, 81.

TABLE 2.—SECONDARY ANEMIA

Diagnosis	Hgb., Per Cent.	R. B. C.	Initial	Complete
1. Carcinomatosis	50	2,904,000	0.525	0.300
2. Addison's disease	80	3,040,000	0.500	0.300
3. Retroperitoneal cancer	60	2,800,000	0.450	0.325
4. Cancer of stomach	75	3,700,000	0.550	0.300
5. Cancer of sigmoid	75	3,686,000	0.425	0.275
6. Cancer of colon	70	4,752,000	0.450	0.275
7. Pyelitis	75	4,352,000	0.425	0.275
8. Chronic nephritis	70	4,157,000	0.425	0.325
9. Cancer of stomach	70	3,936,000	0.450	0.300
10. Ulcer of stomach	50	2,676,000	0.475	0.275
11. Chronic nephritis	55	2,250,000	0.450	0.250
12. Cancer of stomach	55	3,760,000	0.475	0.300
13. Cancer of stomach	70	2,936,000	0.450	0.300
14. Myxedema	70	4,224,000	0.450	0.325
15. Pylephlebitis	75	4,500,000	0.425	0.325
16. Cancer of stomach	60	2,688,000	0.450	0.300
17. Nose bleed	65	3,440,000	0.475	0.275
18. Myxedema	70	5,332,000	0.475	0.350
19. Malaria	55	2,408,000	0.450	0.350
20. Debility	55	3,920,000	0.475	0.375
21. Arteriosclerosis	60	2,856,000	0.450	0.225
22. Syphilis	70	3,880,000	0.500	0.375
23. Chronic nephritis	55	3,080,000	0.475	0.375
24. Myxedema	70	3,656,000	0.450	0.375
25. Paroxysmal hemoglobinuria	..	.....	0.450	0.300
Average	..	.....	0.475	0.322

TABLE 3.—PERNICIOUS ANEMIA

	Hgb., Per Cent.	R. B. C.	Initial	Complete
1	55	1,696,000	0.550	0.400
2	40	1,376,000	0.475	0.300
3	65	2,896,000	0.500	0.300
4	70	2,000,800	0.500	0.325
5	55	1,680,000	0.475	0.300
6	30	1,200,000	0.475	0.325
7	55	2,832,000	0.450	0.325
8	75	3,000,000	0.450	0.325
9	70	2,500,000	0.475	0.300
10	60	2,215,000	0.400	0.275
11	60	2,760,000	0.475	0.300
12	25	800,000	0.475	0.250
13	50	1,344,000	0.475	0.325
Average			0.477	0.322

TABLE 4.—MISCELLANEOUS

Diagnosis	Hgb., Per Cent.	R. B. C.	Initial	Complete
Splenic anemia	0.50	3,200,000	0.500	0.275
Splenic anemia	0.50	4,000,000	0.500	0.200
Banti's disease	0.70	3,108,000	0.475	0.375
Chronic family jaundice	0.80	4,120,000	0.600	0.400
Obstructive jaundice	....	.....	0.400	0.225
Obstructive jaundice	....	.....	0.400	0.175
Obstructive jaundice	....	.....	0.425	0.275

there is no increase of resistance; quite the contrary. The average points of hemolysis for the secondary anemia cases were, 0.475 (initial), 0.322 (complete). The highest initial hemolysis was at 0.550, the highest complete hemolysis at 0.375. The lowest initial hemolysis was at 0.425; the lowest complete at 0.250. It will thus be seen that there are apparently no assured and constant values for the points of initial and complete hemolysis in the blood from cases of secondary anemia, although in general, the tendency is as stated above.

PERNICIOUS ANEMIA

Blood from 13 patients with pernicious anemia was examined. Several of these patients had previously had arsenic in some form, but most of them had had none for at least six months previous to testing their blood fragility. One case only had had salvarsan four days before the fragility test was done on his blood. This is important to note, for as will be shown later, arsenic may have a good deal of influence on the fragility.

The average for the pernicious anemia cases was 0.477 (initial), 0.322 (complete). The highest figures were 0.550 (initial) and 0.400 (complete). The lowest figures were 0.400 (initial) and 0.250 (complete). It will thus be seen that the average is about the same as for secondary anemia, but there may be more variation in the individual cases. It is interesting to note the case which showed the greatest fragility 0.500 (initial) 0.400 (complete). The patient was an Armenian woman with an easily palpable spleen and liver, and a great deal of brownish pigmentation. The blood picture was quite characteristic of pernicious anemia, with many megaloblasts and normoblasts, many macrocytes and microcytes, and much polychromatophilia and stippling. It corresponds very closely to the type of case to which Moffit has called attention, in which the picture is such that no other diagnosis than pernicious anemia is possible, but in which the spleen is much larger than in the ordinary case, with a good deal more pigmentation of the skin than is usually seen, and an increased blood fragility, somewhat approaching the type of anemia sometimes found in cases of chronic family jaundice.

Cases of splenic anemia, myelogenous and lymphatic leukemia, Banti's disease, chronic family jaundice, and obstructive jaundice were studied, but not enough cases of each group to warrant drawing any definite conclusions.

The figures for obstructive jaundice agree with those of other investigators; there is always a greatly increased resistance in obstructive jaundice, which may be due to the fact that the serum of jaundiced patients is hypertonic (it has been shown that by immersing red blood

cells in hypertonic solutions, the resistance can be increased), or to the fact that the cholesterin in the jaundiced serum may have a direct inhibitory effect on hemolysis. The fragility test is of practical value as a corroborative test in differentiating between obstructive and hemolytic jaundice, for as far as I know, there is always increased resistance in the former, and decreased in the latter.

It has been said that the hemoglobin content of the cell is the factor which governs cell fragility; with a low hemoglobin percentage there is a high resistance, and as the hemoglobin increases, the resistance decreases (Strasser and Neumann[14]).

It will be seen from the tables that this does not hold for the cases reported here; there is apparently no relation between the hemoglobin content of the cell and its resistance.

To recapitulate: The average points of hemolysis for normal bloods, pernicious and secondary anemias, are:

Normal	0.457 (initial)	0.340 (complete)
Secondary anemia ...	0.475 (initial)	0.322 (complete)
Pernicious anemia ...	0.477 (initial)	0.322 (complete)

THE INFLUENCE OF ARSENIC ON HEMOLYSIS

In 1898, Bettmann,[15] in a very comprehensive research on the effect of arsenic on the blood and blood-forming organs, found that in subacute arsenical poisoning, there was a lowering of resistance. In his work he did not use ordinary medicinal doses, but worked with larger toxic doses. In 1908 Gunn[16] found that immersing red blood cells for an hour in a solution of arsenious acid (1 to 10,000) made them more resistant to hypotonic salt solution. In 1911 Gunn and Feltham[17] continued these experiments and found that arsenic not only had a protective action against hemolysis with hypotonic salt solution, but also protected against hemolysis with cyclamin (a saponin-like substance), and sodium glycocholate. It was thought worth while to continue this work and it was done as follows:

1. A normal blood was run through in the regular way, with the regular amount of salt solution and blood, *plus* 0.05 c.c. 0.7 salt solution in each tube. Initial hemolysis 0.425. Complete hemolysis 0.350.

Then in a second series of tubes the procedure was the same, only substituting 0.05 c.c. of 0.7 c.c. salvarsan solution for the 0.05 c.c. of 0.7 per cent. salt solution. Initial hemolysis 0.425. Complete, 0.325.

In a second test 0.10 c.c. salt solution was used instead of 0.05 c.c. Initial hemolysis 0.425. Complete hemolysis 0.300. When 0.10 c.c. of salvarsan solution was substituted for the salt, the figures were 0.400 (initial), 0.300 (complete).

In these four series there was, it is true, some increase of resistance in the tubes containing salvarsan, as shown by the reading of the initial and complete

14. Strasser and Neumann: Med. Klin., , No. 34.
15. Bettmann: Ziegler's Beitr. zur pathol., Anat., 1898, xxiii.
16. Gunn: Brit. Med. Jour., July 28, 1908.
17. Gunn and Feltham: Brit. Med. Jour., Jan. 21, 1911.

hemolysis, but the most striking thing was that in each pair of corresponding tubes, all down the line from initial to complete, there was *always* much less hemolysis in the tubes containing the salvarsan.

2. Normal blood (0.05 c.c.) + 0.05 c.c. 0.7 per cent. salvarsan solution + 0.5 c.c. distilled water — *nearly complete hemolysis.*

Normal blood (0.05 c.c.) + 1.05 c.c. 0.7 per cent. salvarsan solution + 0.5 c.c. distilled water — very slight hemolysis.

3. Anemic blood (0.05 c.c.) + 0.05 c.c. 0.5 per cent. salt solution in each tube, 0.475 (initial), 0.400 (complete).

Same blood (0.05 c.c.) + 0.05 c.c. 0.05 per cent. Fowler's solution (potassium arsenite) substituted for the 0.05 c.c. of salt solution, 0.400 (initial), 0.275 (complete).

Syphilitic blood (0.05 c.c. + 0.05 c.c. 0.5 per cent. salt solution in each tube, 0.450 (initial), 0.375 (complete).

Same blood (0.05 c.c.) + 0.05 c.c. 0.5 per cent. Fowler's solution substituted for the 0.05 c.c. of salt solution, 0.375 (initial), 0.275 (complete).

These results with Fowler's solution are very striking, and clearly prove that in vitro, at any rate, arsenic has a very definite inhibitory effect on hemolysis. In vivo the results are not quite so striking, but show the same thing to a less degree.

In 4 cases of syphilis, the fragility of the blood was tested before and after 0.3 gm. of salvarsan intravenously. There was exactly the same resistance before as after; the arsenic given had no effect whatever on the fragility. The amount of arsenic, however, in the 6 c.c. of blood taken for examination, is so infinitesimal (about 0.0006 gm.), that it could hardly be expected to influence the fragility.

In 3 cases of pernicious anemia treated with several doses of salvarsan the results were as follows:

1. Before salvarsan.....	0.475	(initial)	0.300 (complete)
After seven doses of salvarsan	0.400	(initial)	0.275 (complete)
2. Before salvarsan	0.450	(initial)	0.325 (complete)
After five doses of salvarsan	0.425	(initial)	0.350 (complete)
3. Before salvarsan	0.400	(initial)	0.275 (complete)
After four doses of salvarsan.	0.450	(initial)	0.275 (complete)

It is interesting to note that the general condition, and the red count and hemoglobin of the first two cases rose during the salvarsan treatment, and were unchanged in the third case.

4. A case of pernicious anemia was given Fowler's solution for ten days, starting with 5 drops three times a day, and increasing 3 drops a day, until he was getting 36 drops in the twenty-four hours.

The blood was examined before and after the course of Fowler's solution.

Before	0.475	(initial)	0.325 (complete)
After	0.450	(initial)	0.275 (complete)

It would seem from the figures that arsenic in medicinal doses has a definite inhibitory action on hemolysis, *and it may well be that the beneficial effect of arsenic in the anemias is due rather to a prevention of hemolysis than to a stimulant effect on the bone marrow, a view which has been held by some writers.*

CHANGES IN FRAGILITY AFTER SPLENECTOMY

Pel,[18] in 1912, found in splenectomized dogs that there was an increased resistance of the red cells to hypotonic salt solution after splenectomy. Karsner and Pearce[19] confirmed this. As far as I know, there are no data concerning fragility changes after splenectomy in human beings. About the time that this work was being done, a number of ward patients with pernicious anemia were operated on, with removal of the spleen. The blood fragility of these patients was studied before and after operation.

1. Before splenectomy	0.475 (initial)	0.300 (complete)
8 days after splenectomy...	0.450 (initial)	0.275 (complete)
21 days after splenectomy...	0.500 (initial)	0.250 (complete)
2. Before splenectomy	0.475 (initial)	0.300 (complete)
15 days after splenectomy....	0.450 (initial)	0.275 (complete)
50 days after splenectomy....	0.700 (initial)	0.225 (complete)
3. Before splenectomy	0.475 (initial)	0.250 (complete)
15 days after splenectomy....	0.475 (initial)	0.250 (complete)

These figures are somewhat contradictory, but in three of the cases the greatly increased resistance of some of the cells, as shown by the low figures for complete hemolysis, was striking. It was noted in all these cases that a good many cells with the so-called "Jolly bodies" appeared in the blood after splenectomy. It is possible that these cells may have been the cause of the increased resistance.

CONCLUSIONS

1. The resistance of normal blood to hemolysis by hypotonic salt solution is fairly constant.

2. The figures for pernicious anemia and for secondary anemia are practically the same. In any given case of anemia, whether primary or secondary, the resistance may be high, normal, or low; there is no such constant finding as there is in normal blood. In general, in both pernicious and secondary anemia, hemolysis is likely to begin sooner and end later than it does in normal blood.

3. The hemoglobin content of the cell seems to bear no relation to its resistance.

4. Arsenic definitely increases the resistance of the red cells and tends to inhibit hemolysis.

5. Splenectomy increases the maximal resistance; it may decrease the minimal resistance.

I wish to express my thanks to the members of the visiting staff for their interest during the course of the work, and for their many helpful suggestions.

18. Pel: Deutsch. Arch. f. klin. Med., 1912, cvi, Nos. 5 and 6.
19. Karsner and Pearce: Jour. Exper. Med., 1912, xvi, 769.

A STUDY OF A CASE OF AURICULAR FLUTTER*

SAMUEL A. LEVINE, M.D., AND C. FROTHINGHAM, JR., M.D.
BOSTON

In 1887 McWilliam[1] produced a flutter in the auricles of the mammalian heart by means of faradic stimulation of the auricles. In 1908 Hertz and Goodhart[2] reported a human case in which the auricles were beating rapidly at a rate of about 230 per minute, but the ventricles were beating about 80. In 1911, Jolly and Ritchie[3] applied the term of auricular flutter to those cases of rapid regular auricular contractions ranging from 250 to 350 per minute associated with partial or complete heart block, so that the ventricular rate was much slower.

Reports of similar cases have appeared in the medical literature since that time. Summaries of these cases with the addition of new ones have been made by Lewis[4] in 1912, and more recently by Ritchie[5] in 1914. At present this cardiac condition is well recognized as a clinical entity, and appears in the modern textbooks on cardiac diseases such as Lewis'[6] "Clinical Disorders of the Heart Beat," Cowan's[7] "Diseases of the Heart" McKenzie's[8] "Diseases of the Heart," and Osler and McCrae's[9] most recent edition of "Modern Medicine."

Auricular flutter is looked on as a regular rapid action of the auricles, in which the origin of the auricular beats is from some point in the auricle other than the normal one in the sinus node. The justification for considering the beat ectopic in origin lies in the fact that

* Submitted for publication April 14, 1915.

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard University.

* This work was done in part under a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

1. McWilliam, J. A.: Fibrillary Contraction of the Heart, Jour. Physiol., 1887, viii, 296.
2. Hertz, A. F., and Goodhart, G. W.: The Speed-Limit of the Human Heart, Quart. Jour. Med., 1908-1909, ii, 213.
3. Jolly, W. A., and Ritchie, W. T.: Auricular Flutter and Fibrillation, Heart, 1910-1911, ii, 177.
4. Lewis, Thomas: Observations upon a Curious and not Uncommon Form of Extreme Acceleration of the Auricle, "Auricular Flutter," Heart, 1912, iv, 171.
5. Ritchie, W. T.: Auricular Flutter, Edinburgh and London, W. Green & Son, 1914.
6. Lewis, Thomas: Clinical Disorders of the Heart Beat, New York, P. B. Hoeber, 1914.
7. Cowan, J.: Diseases of the Heart, Philadelphia, Lea & Febiger, 1914.
8. McKenzie, James: Diseases of the Heart, London, Frowde and Hodder, and Stoughton, Ed. 3, 1914.
9. Osler and McCrae: Modern Medicine, Philadelphia, Lea & Febiger, 1915.

the P wave in the electrocardiograms is abnormal in form. Usually there is some degree of heart block present, but not always. As a rule the ratio between the auricular and ventricular contractions is an even one 2:1, 4:1, or 6:1. Occasionally the ratio is 3 or 5 to 1. The ratio may vary considerably in the same case at different times. The diagnosis is made most easily by means of the electrocardiograph,

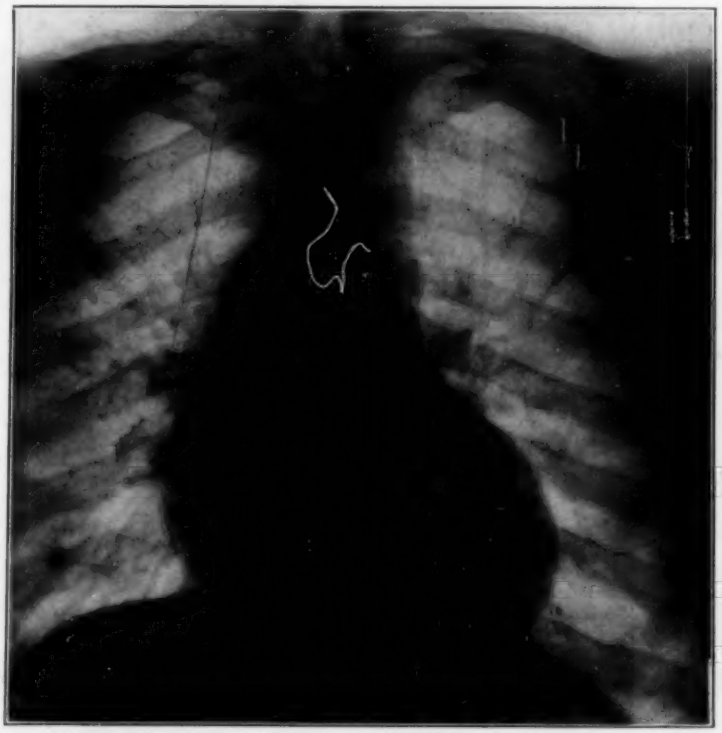


Fig. 1.—Roentgenogram of chest taken Oct. 21, 1914, during an attack of flutter.

but may be made by the polygraph or even by a radial tracing alone, if changes in the ratio of heart block are caught. For as Fulton[10] has emphasized in a recent paper, although the ventricular rate may be irregular, definite time relations will be met, if groups of ventricular beats are taken which are supposed to correspond to the same number of auricular beats.

10. Fulton, F. T.: "Auricular Flutter," with Report of Two Cases, THE ARCHIVES INT. MED., 1913, xii, 475.

This condition of flutter of the auricles is not influenced by the methods, supposed to stimulate the vagus, which are sometimes successful in stopping an attack of tachycardia. After the administration of digitalis the ratio between the auricular and ventricular rates usually increases, then either fibrillation of the auricles or a combination of

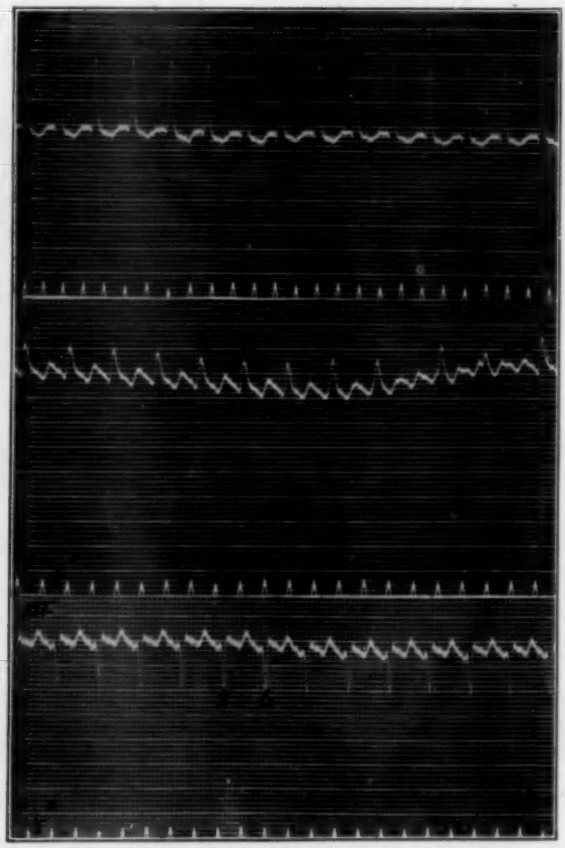


Fig. 2.—Electrocardiograms taken Oct. 22, 1914, of all three leads. They show auricular flutter with a 2:1 heart block and left ventricular hypertrophy. At the end of Lead 2 a break in the 2:1 rhythm is seen.

fibrillation and flutter occurs, and finally the heart returns to its normal rhythm in most cases. Digitalis should be omitted after fibrillation begins.

In many of the cases of flutter reported, more than one attack has been observed. The attacks may last from a few moments to years.

It occurs apparently at any age and associated with a variety of clinical conditions. The symptoms accompanying flutter are not always constant. Probably they are so slight in some cases that the condition passes unobserved. No constant pathologic lesion has been found in the cases that have come to necropsy, but diffuse degeneration of the auricular musculature or involvement of the sino-auricular and auriculo-ventricular nodes has been met.

Although auricular flutter is now well recognized there are many points of practical and scientific interest in regard to this condition which are as yet unsettled. One question of interest is whether the P wave in the electrocardiogram is elevated or depressed in the different leads. The relation between this abnormal rhythm and organic lesion of the heart is still undecided and will remain so until much more necropsy material has been studied. In many of the cases reported the flutter has occurred in hearts in which disease of the mitral valve existed. Is the condition due to one special lesion of the auricles or nerves, or may it be associated with a variety of cardiac lesions? Reports on Roentgen-ray studies during and after an attack are rare, as are also studies on the pulse pressure during the attacks.

During the past winter a case of auricular flutter was under observation in the medical outdoor department and wards of the Peter Bent Brigham Hospital. The study of this case has brought out several points of interest in regard to auricular flutter, and therefore it seems advisable to report it. The following summary of the case is obtained from the records of the outdoor department, the ward records, and notes made by one or the other of us.

The patient, an unmarried Bulgarian, aged 35 (hospital medical number, 1791), entered the hospital Oct. 20, 1914, complaining of stomach trouble and shortness of breath.

The family history was unimportant. His past history revealed that at the age of 17 he had tonsillitis for one month. At the age of 18 he had a septic finger with an extension of the inflammation up the arm. At the age of 33 he had another attack of tonsillitis with slight stiffness in the elbow suggesting rheumatism. No history of other diseases, even the ordinary ones of childhood, could be obtained. He had never suffered from shortness of breath before. He fought through the Balkan war in 1913. All venereal disease was denied. He did not use alcohol, drugs, or tea. Formerly he had used considerable coffee but not for some years. Tobacco was limited to one cigar a day.

Twelve days before entrance, the patient noticed rheumatic pains in his shoulders and arms due, he thought, to working in a cold cellar on the preceding day, after taking a hot bath. The pain was not severe enough to stop his work. On the following day he noticed a peculiar feeling about his heart. He could feel the heart strike forcibly against his ribs with some discomfort, but no actual pain. He noticed that the action of his heart was irregular. Six days before entrance he found that he became slightly short of breath on exertion. This increased somewhat up to the time of entrance into the hospital. Otherwise he felt well and was able to lie flat in bed without discomfort.

Physical examination revealed an unusually well-developed short man with good color and rugged appearance. The head, eyes, ears, and nose were normal. The teeth were in good condition, and the throat negative. Except for rapid pulsations, the neck showed nothing abnormal. The lymph glands of the body were not enlarged. The lungs presented no abnormal signs. The abdomen was soft and free from masses. The liver and spleen were not felt. No edema was

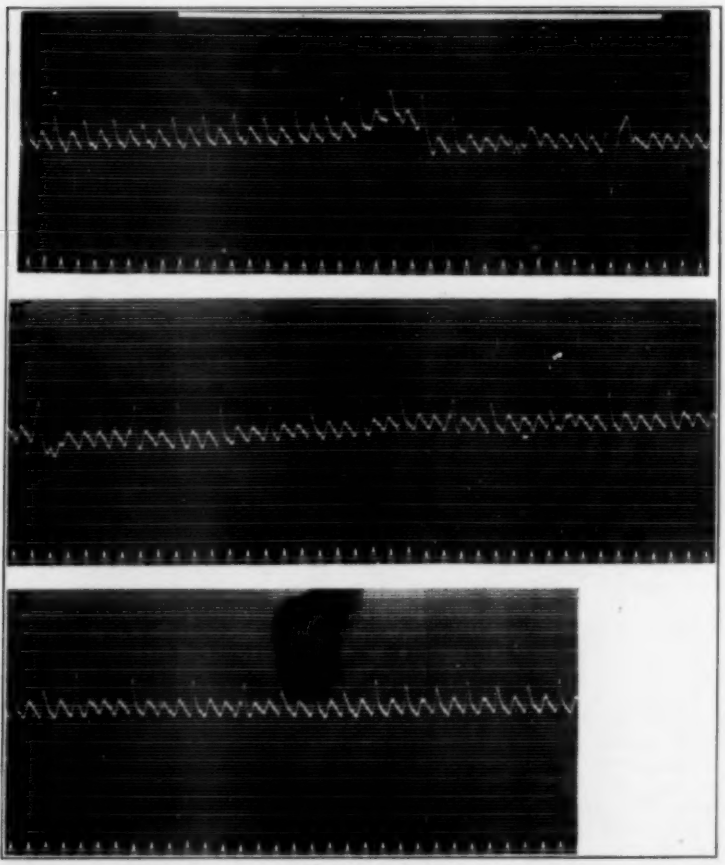


Fig. 3.—Lead 2, Oct. 20, 1914. The three strips represent a continuous tracing. Signal at top marks the duration of left ocular pressure. Marked inhibition of the ventricles occurs and extra systoles appear.

present in the extremities and the reflexes were normal. The peripheral vessels were not rigid or tortuous.

When the heart was examined the apex was seen to be beating rapidly. The point of maximum impulse was in the fifth space, 12 cm. to the left of the midsternal lines. The left border was 13 cm. to the left of the midsternal line in the sixth space, and the right border was 3 cm. to the right of the midsternal

line in the fourth space. The heart was beating regularly and at the rate of 176 per minute. No thrills were felt. Auscultation revealed a faint systolic murmur at the apex following the first sound. The murmur was followed by a second sound. This murmur was heard all over the precordia and became louder and rougher on approaching the aortic area. No other abnormal heart sounds were heard. The blood pressure by the house officer was 104 systolic and 60 diastolic.

The blood examination, including the Wassermann reaction, was negative. The urine showed a specific gravity of 1.026, a slight trace of albumin, no sugar, an occasional granular cast and pus cell, but no blood.

The report of the Roentgenologist[11] on examination of the patient at this time by fluoroscope and roentgenogram states that there is a diffuse dilatation in the region of the descending aorta. Rapid pulsations were seen in this area. The right side of the heart was slightly increased in size, especially in the region of the right auricle. The entire right side of the chest was hazy in comparison to the left. Figure 1 shows the position of the heart and its size during an attack of flutter.

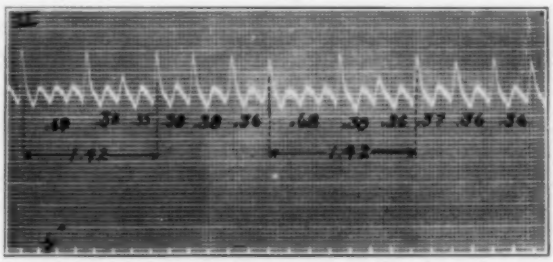


Fig. 4.—Lead 2, Oct. 27, 1914. This shows the increase in degree of auriculoventricular block following digitalis, also the grouping of the ventricular beats.

Electrocardiographic study at this time showed an auricular flutter with a fairly constant auriculoventricular 2:1 rhythm. The auricles were beating 342.8 times per minute, and the ventricles 171.4 times. The electrocardiograms also presented evidence of left ventricular hypertrophy, as may be seen in Figure 2. Lead 1 (from right to left arm) in Figure 2 shows a steep initial ventricular complex marked R and a slight negative T wave as the final ventricular deflection. Just before R there is a slight elevation, probably the P wave, due to auricular disturbance. Lead 2 (from right arm to left leg) in Figure 2 shows the triangular form of the P waves so characteristic of flutter. The ventricular complexes are complicated by the superimposed P waves, thus modifying the R and T deflections. Toward the end of this tracing the ventricles break their rhythm while the auricular complexes continue regularly. The electrocardiogram here shows that the auricles have been beating twice as rapidly as the ventricles. Lead 3 (from left arm to left leg) in Figure 2 shows a deep S wave as the initial ventricular deflection, which together with the prominent R wave in Lead 1, denotes left ventricular hypertrophy. There is slight notching in the downstroke of the auricular complex.

In order to bring out more clearly the rapid auricular rate, vagal pressure was tried with the hope of inhibiting the ventricles, but without success. As

11. For the roentgenograms we are indebted to Dr. G. L. Carr.

Levine[12] has shown that the oculocardiac reflex which was first described by Aschner,[13] is more effective than direct pressure on the vagi in causing vagal inhibition, pressure was applied to the left eyeball of this patient for five and five-tenths seconds. Although it did not have any appreciable effect on the auricular rate, it did cause an inhibition of ventricular contractions after a latent period of three seconds. The electrocardiogram (Fig. 3) at this time therefore shows more clearly than those in Figure 2, that the auricles are contracting regularly at a rate of about 340 per minute.

Fig. 5.—Roentgenogram of chest taken Oct. 29, 1914, during normal rhythm.

In Figure 3 it is seen that twenty-five successive auricular beats following the beginning of the inhibition failed to produce a normal ventricular contraction. During that time three ventricular complexes appear, each different from the other and from the normal, which show that they started from different foci in the ventricles. Two seconds after the release of ocular pressure, a 3:1

12. Levine, S. A.: The Oculo-Cardiac Reflex. An Electrocardiographic Study with Special Reference to the Difference Between Right and Left Vagal and Ocular Pressure in Tabetics and Non-Tabetics, THE ARCHIVES INT. MED., 1915, xv, Part 1, p. 758.

13. Aschner, B.: Ueber einen bischer noch nicht beschriebenen Reflex vom Auge auf Kreislauf und Atmung, Wien. klin. Wchnschr., 1908, xliv, 1529.

auriculoventricular rhythm was started and twelve seconds after the release of pressure the rhythm returned to the 2:1 ratio which existed before the pressure was instituted.

Pressure on the right eyeball for eight and five-tenths seconds produced inhibition of the ventricle after a latent period of three seconds, which lasted over 43 auricular beats. During this time there were seen seven ectopic ventricular complexes, some of which varied in form from each other. From these different observations and examinations the diagnosis of auricular flutter was made, and some organic disease of the heart was suspected.

The patient felt so well that he refused to stay in the hospital another night, but agreed to come in for daily observation. Digitalis 0.1 gm., three times a day, was begun on October 24, the first day he returned to the out-door department after leaving the hospital. On the 27th, when he had taken in all 1 gm. of the digitalis leaves, the electrocardiogram showed an increase in the degree of heart block (Fig. 4).

From Figure 4 it is clear that the number of ventricular beats in relation to the auricular systoles varies from a 2:1 ratio to a 4:1 ratio. This electrocardiogram demonstrates the point mentioned above, that the ventricular beats, although irregular in rhythm, show a definite time relation to each other if taken in groups corresponding to an equal number of auricular contractions. Thus in this curve it is seen that two sets of ventricular beats in different parts of the tracing although irregular in rhythm, but each corresponding to eight auricular beats, are equal in length. This is peculiar to flutter in contrast with other forms of irregularity with rapid rate. It is also evident that there is a slight variation in the size of the ventricular deflection which suggests pulsus alternans. This is especially pronounced after an extra long pause in the ventricular complexes, denoting a condition similar to the pulsus alternans seen in some cases following extra ventricular systoles. The pulsus alternans observed during flutter with rapid ventricular rate is not considered of so much prognostic value as that occurring in slowly beating hearts.

When he came under observation on October 29, two days later, having had, in all 1.5 gm. of digitalis, his heart action was slow and regular. In this patient, therefore, the intermediary stage of auricular fibrillation which usually occurs between flutter and normal rhythm was not observed.

Examination at this time showed the cardiac boundaries 14 cm. (12.5 cm. tangentially) to the left of the midsternal line in the sixth space, and 4 cm. to the right of the midsternal line in the fourth space. A systolic thrill, which was not made out during flutter, was now palpable over the precordia and the neck, most distinctly in the second interspace to the right of the sternum. On auscultation a rough systolic murmur was heard over the whole precordia, loudest in the aortic area, and transmitted to the vessel of the neck. A faint diastolic murmur was heard following the second sound in the aortic area and faintly over the precordia. No pistol-shot sound was heard in the femoral arteries.

The roentgenogram (Fig. 5) taken at this time showed no change in the size or shape of the heart from its appearance during the attack of flutter. The electrocardiogram (Fig. 6) showed a regular slow auricular rhythm of about 75 per minute. As a rule a normal ventricular complex followed the auricular beat after a slightly prolonged interval, showing a delayed conduction time, possibly due to digitalis. Also there was noted in the electrocardiogram, extra ventricular systoles starting from some ectopic focus. These premature systoles occurred so near the time for the regular beat that they came after the P wave in the electrocardiogram in most cases. The variation from the normal rhythm was so slight that it was not detected in palpating the radial pulse.

These examinations show that the organic heart disease suspected during the attack of flutter consists in a lesion of the aortic valve causing stenosis and slight regurgitation.

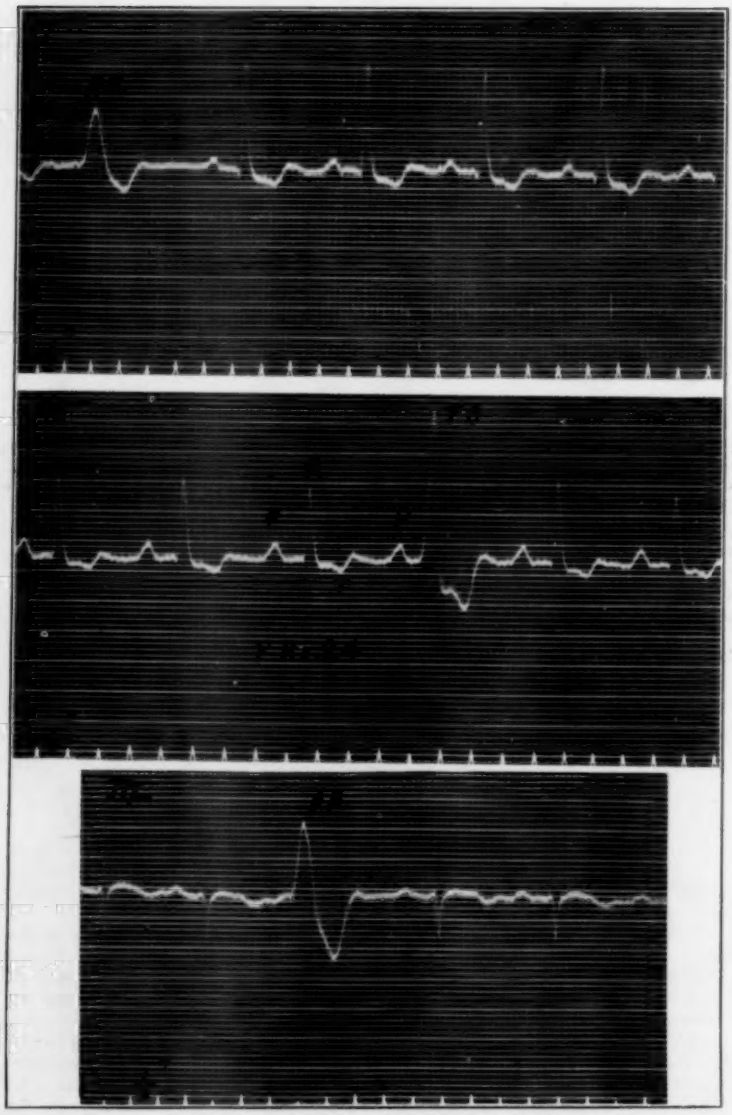


Fig. 6.—Electrocardiograms taken Oct. 29, 1914, of all three leads. It shows normal rhythm with extra ventricular systoles (marked P B) and a delayed conduction time (P-R interval 0.24 second).

From October 29 to February 5 the patient was observed occasionally and he reported that at times he was taking digitalis. No reliable information in regard to the digitalis was obtained. On February 5 the patient was found to have another attack of flutter. He stated that in the afternoon of February 2 his heart started to beat rapidly. At that time he had pain in the left ankle and both shoulders. When seen on the 5th his temperature was 99.4 F. Physical examination, fluoroscopic study, and roentgenograms showed no change from the former attack of flutter. Blood pressure observations at this time showed an average systolic pressure of 92 mm. of mercury and a diastolic pressure of 80. Tracings from the jugular vein and brachial artery were recorded simultaneously with the electrocardiograms as shown in Figure 7 demonstrating an auricular rate of 336 per minute and a ventricular of 168, a definite 2:1 rhythm. The triangular appearance of the P wave in Lead 2 is again evident with the notch in the down stroke of the P wave, as mentioned above. In the brachial tracing the alternating character of the pulse observed in the ventricular complexes of Figure 4 is seen. In the jugular tracing the "*a*" and "*c*" waves are evident but not the "*v*" waves.

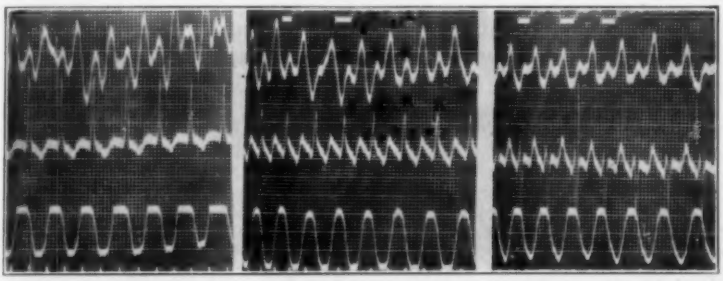


Fig. 7.—Jugular and brachial tracings taken simultaneously with the electrocardiograms on Feb. 5, 1915. Jugular above and brachial tracing below the electrocardiogram. They show auricular flutter with a 2:1 heart block. Alternation of the ventricle is evident in the brachial and electrical tracings. (The flat top in the brachial tracing of Lead 1 is due to a mechanical artifact.)

At this time salicylates were given and also digitalis. After he had taken 0.3 gm. of digitalis leaves he noticed at 3 p. m. that his heart became slower and jumping. This condition persisted until he went to sleep at 9 p. m. At 4 a. m. the next morning he awoke with his heart apparently normal.

The accompanying electrocardiogram (Fig. 8) shows the three leads taken that day with the heart beating normally. The rate is about 100. The interesting feature is the prolonged P-R interval which denotes a delay in the conduction of the impulse from auricle to ventricle. This interval is 0.25 second which is above the upper limit of the normal. This of course may be due to the digitalis which he had been taking and therefore no conclusions can be drawn from it.

Blood-pressure observations were made at this time. An average of several readings showed that the systolic pressure was 90 mm. of mercury, the diastolic 69, making the pulse pressure 21. These readings showed that during the attack of flutter the pulse pressure diminished. Table 1 gives the blood pressure observations during flutter and during normal rhythm. The patient soon afterward dropped out of sight and was reported to have gone back to Bulgaria.

Other points of interest in regard to auricular flutter were brought out at different times in this study. In paroxysmal tachycardia the auricles are apparently under the influence, to some extent, of the vagus. In flutter, however, the auricles are supposed to be very little influenced, if at all, by the methods that are thought to call forth stimulation of the vagus. In this case it has been shown above that ocular pressure inhibited the ventricles. This and such other methods of affecting the vagus, as drinking iced water, pressure on the vagus in the neck, and deep breathing, varied in their action on the auricular rate. No effect was obtained from drinking iced water. By some of the other methods slight but not constant variations in the auricular rate were obtained. In deep breathing a slight but constant slowing of the auricles occurred. This seemed worthy of mention, because normally in flutter, for long periods, the rate for groups of ten beats does not vary more than one or two hundredths of a second. During or

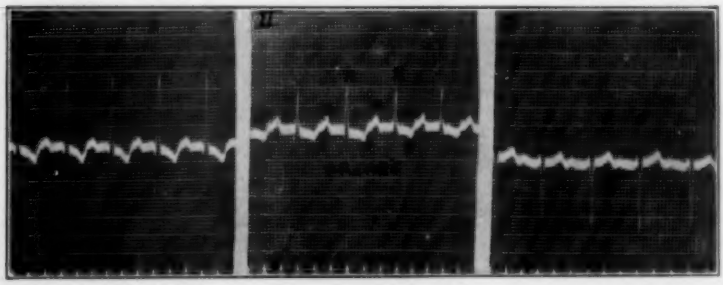


Fig. 8.—Electrocardiogram taken Feb. 6, 1915. It shows normal rhythm with delayed conduction time (P-R interval 0.25 second).

just after deep breathing the rate slowed from 348.8 to 338.3 per minute, or a variation of four or five hundredths of a second in consecutive groups of ten beats. Table 2 shows how constant the time relations are normally for groups of ten auricular beats and the slight but definite slowing produced by the deep breathing. Thus it seems probable that the vagus still has some slight control of the auricles in flutter.

It has been noted that the duration of the electrical disturbance created by the auricular contraction in flutter is relatively long in Leads 2 and 3. It is seen in Figure 3 when the ventricles were inhibited, that this auricular action is so prolonged that one P wave runs up to the beginning of the next, that is, there is a continuous change in the electrical potential. There has been considerable discussion as to the nature of the P wave in flutter in Leads 2 and 3. Ritchie[5] in his book

speaks of the P wave as upright and often diphasic. Lewis[6] says they are probably upright.

By means of the simultaneous venous tracings and electrocardiograms it was thought some light might be thrown on this point. Lewis has calculated that normally there is a P-a interval of about eight hundredths of a second between the beginning of the P wave in the electrocardiogram and the start of the "a" wave in the neck. Assuming that the P-a interval in flutter was the same as in normal conditions, we measured back in Figure 7 eight hundredths of a second from the

TABLE 1.—Blood Pressure Observations *

During flutter, Feb. 5...	94-84-10	96-82-14	96-82-14	90-74-16	92-78-14	86-78-10	Aver. 92-80-12
During normal rhythm Feb. 6	90-72-18	90-70-20	90-65-25	.....	.....	.....	Aver. 90-69-21

* The three figures are the systolic, diastolic and pulse pressures respectively.

TABLE 2.—Duration in Seconds of Groups of Ten Auricular Beats Taken Consecutively

Normal, Oct. 20, a. m.	1.74	1.73	1.74	1.74	1.74	1.74				
Normal, Oct. 20, p. m.	1.70	1.72	1.71	1.70	1.70	1.70	1.70			
Normal, Oct. 22, p. m.	1.74	1.74	1.74	1.74	1.75	1.75	1.75	1.75	1.75	1.74
Held deep inspiration, Oct. 20, a. m.	1.73 *	1.77	1.78	1.78	1.78 *	1.72	1.74	1.73	1.73	1.74
Held deep inspiration, Feb. 5, a. m.	1.79 *	1.80	1.81	1.80	1.80	1.82	1.82 *	1.83	1.83	1.81	1.80

* Deep inspiration held by the patient, resulting in more marked variation than in the normal.

TABLE 3.—Amplitude of the Respective Waves in Millivolts *

	Lead I				Lead II				Lead III				P-R	R-T
	P	R	S	T	P	R	S	T	P	R	S	T		
Flutter	0.05	1.8	—	−0.2	−0.35 +0.35	1.2	—	?	−0.25 +0.25	0.1	1.2	?	0.26	0.21
Normal rhythm	0.3	2.0	—	−0.4	0.4	1.1	—	0.1	0.1	0.1	1.6	0.3	0.25	0.28

* The P-R and R-T times are measured in seconds as represented by the figures in Leads 1, 2 and 3.

beginning of the "a" wave in the jugular tracing and found that the point came at the notch on the down stroke of what was supposed to be the P wave. Of course the question may be raised as to whether the point from which we measured was the beginning of the "a" wave. Our feeling that such was the case was increased on examination of another electrocardiogram in Lead 2, in which, due to a break from 2:1 to a 4:1 rhythm, there was no doubt in regard to a certain wave being an "a" wave. By measuring back eight hundredths of a second

in this tracing the notch in what has been called the down stroke of the P wave was again met. It seemed more reasonable therefore to call this point the beginning of the P wave, to consider the wave diphasic, and to look on the notch as the junction between the preceding P wave and the beginning of the next one. However, another weak point in this contention is that it is not perfectly established that the beginning of the P wave in flutter occurs eight hundredths of a second before the beginning of the "a" wave in the jugular, as it does normally.

A study was also made of the height of the waves in the different leads and the length of the P-R interval and the R-T interval during an attack of flutter and when the heart was in normal rhythm. These results are summarized in Table 3. In all three leads it will be seen that the amplitude of the R and S waves are only slightly changed from the normal during flutter. In Lead 1 the T wave is slightly higher during the normal rhythm. In Leads 2 and 3 no conclusion can be reached with regard to the T waves, because their form was obscured by the superimposed P waves. In Lead 1 the P wave is much diminished in height during flutter, while in Leads 2 and 3 the total of the up and down deflections of the P wave shows a marked increase over the normal. Each up or down deflection, however, was nearly equal to the height of the normal P wave. The P-R interval remained the same during the attacks as when the heart was beating in normal rhythm, but the R-T time showed considerable diminution during the flutter.

SUMMARY

Auricular flutter was observed twice in a man with organic disease of the aortic valve consisting in stenosis and slight regurgitation. Opportunity was given to study him during and between attacks by means of the electrocardiograph and also by tracings from the jugular vein and brachial artery, taken simultaneously with the electrocardiogram.

In this man the auricular rate during flutter varied at different times from 350.5 per minute to 324.7 per minute. The ventricles were beating most of the time during the attacks at half that rate showing a 2:1 block.

During the attack of flutter the auricles were practically independent of vagus control, although a slight effect on the auricular rate could be produced by deep breathing. The ventricles could be inhibited by pressure on either the right or left eye, but the auricles could not be inhibited. During the attack of flutter there was slight pulsus alternans as shown in both the electrocardiogram and brachial tracings. This

disappeared when the heart returned to its normal rhythm. The amplitude of the T wave was diminished in Lead 1, the duration of the ventricular cycle (R-T interval) was shortened, and in Leads 2 and 3 the P waves were much increased in amplitude.

Roentgenograms showed no appreciable difference in the outline of the heart during the attack, and the pulse pressure, which was small normally in this case, diminished during flutter. In this case of flutter the P wave in Leads 2 and 3 is probably diphasic and the notch on the downstroke of the auricular complex is the junction between two P waves.

SINO-AURICULAR HEART BLOCK

WITH REPORT OF A CASE IN MAN *

J. A. E. EYSTER, M.D., AND J. S. EVANS, M.D.
MADISON, WIS.

While abnormalities in conduction and partial or complete blocking of the cardiac impulse at the auriculoventricular junction is a fairly frequent clinical condition, similar disturbances at the sino-auricular junction are apparently exceedingly infrequent in the higher animals and in man. So far as we have been able to find, only four clinical cases in which the diagnosis was satisfactory have been reported. The first case was reported by Mackenzie[1] in 1902, in a patient during an attack of influenza. The second case was reported by Wenckebach[2] in 1906, in a man, aged 30, who was apparently normal aside from the disturbance in the heart rhythm. The third case, described by Hewlett[3] in 1907 and the fourth by Rihl[4] in 1908 were in cases of advanced cardiac and arterial disease.

In all of these the diagnosis was made by the aid of the venous pulse and rests on the dropping of "a" waves in an otherwise regular auricular rhythm. In all, the sino-auricular block was associated with auriculoventricular block. In Mackenzie's case the dropping of auricular beats occurred during complete auriculoventricular block, while in Wenckebach's case each dropped auricular systole was always preceded by a dropped ventricular beat. Hewlett's and Rihl's cases were associated with partial auriculoventricular block, and in the latter the dropped auricular cycle frequently followed a blocked ventricular cycle as in Wenckebach's case. In these two cases the sino-auricular block was noted only after the administration of digitalis. Mackenzie ascribes the condition in his case to the toxemia. Wenckebach's case was in an apparently normal man who came to the clinic only for research purposes. No statement of clinical examination other than the interpretation of the jugular curves is given. Hewlett's case was in a 44 year old alcoholic with pleuritic adhesions, arteriosclerosis and

* Submitted for publication May 29, 1915.

* From the Physiological Laboratory and the Medical Clinic of the University of Wisconsin.

1. Mackenzie: Brit. Med. Jour., 1902, ii, 1911.
2. Wenckebach: Arch. f. Anat. u. Physiol., 1906, p. 297.
3. Hewlett, Albion Walter: Digitalis Heart Block, Jour. Am. Med. Assn., 1907, xlviii, 47.
4. Rihl: Deutsch. Arch. f. klin. Med., 1908, xciv, 286.

liver cirrhosis. Rihl's case was in a woman, aged 63, who showed valvular lesions and advanced arteriosclerosis.

Two cases, described by Joachim[5] in 1905, and one case described by Danielopolu[6] in 1913, were probably not sino-auricular but auriculo-ventricular block, since "a" waves apparently occur between the normal beats on the venous pulse curves published in these articles. The curves in each case are very difficult to interpret because of the exceedingly weak pulsations shown.

Since the activity of the auricle is the first feature of the cardiac contraction which finds expression in the venous pulse curve or electrocardiograph in man,[7] the only criterion of sino-auricular block

5. Joachim: Deutsch. Arch. f. klin. Med., 1905, xcv, 373.

6. Danielopolu: Arch. d. Mal. du Coeur, des Vaissaux et du Sang, 1913, vi, 792.

7. Gibson (The Practitioner, 1907, lxxviii, 589) described a wave on the venous pulse in a clinical case which he designated as the "s" wave and ascribed to contraction of the musculature of the vena cava preceding the auricular contraction. This is probably the same wave described by Hirschfelder (Bull. Johns Hopkins Hosp., 1907, xviii, 265) under the designation "h" and ascribed by him to temporary closure of the tricuspid valve in mid-diastole at the end of the period of most rapid ventricular filling. Eyster (Jour. Exper. Med., 1910, xii, 257) showed that this wave was a normal event of the venous pulse record in slow heart rate and was evidently from its position in cycles of varying length, a diastolic and not a presystolic event. He further showed that in the dog no wave occurred on the venous pulse that could be ascribed to contraction of the mouths of the superior vena cava even when an extra systole was initiated by stimulation of this region. A wave on the venous pulse curve ("x" wave) described by Eyster (see above) following the "h" wave in slow heart rates was apparently also a diastolic feature and unassociated with any possible contraction of the venous or sinus region of the heart. Subsequent work by Thayer (Boston Med. and Surg. Jour., 1908, clviii, 713) showed the close association of the "h" wave with the so-called shoulder on the volume curve of the mammalian ventricle, the point which marks the end of the period of rapid ventricular filling, and Eyster (Jour. Exper. Med., 1911, xiv, 594) found that it occurred practically coincident with the third heart sound as recorded by the microphone and string galvanometer. These facts tend to confirm the diastolic nature of this wave and to render probable the explanation of its cause advanced by Hirschfelder and Thayer. Rehfish (Arch. f. Anat. u. Physiol., 1906, Sup., p. 152) found on the suspension curves of the auricles, in the exposed heart of the rabbit and dog, a small wave preceding the main movement resulting from auricular systole which he referred to contraction of the sinus region of the heart. The interpretation would seem to be at best exceedingly doubtful.

The region of the heart which recent work has shown as the normal seat of impulse initiation, the sino-auricular node, is closely associated anatomically and physiologically with the right auricle. Electrocardiographic methods have shown that activity in this region normally precedes activity in the right auricle by 0.03 second or less in the dog's heart (Eyster and Meek, The Interpretation of the Normal Electrocardiogram, THE ARCHIVES INT MED., 1913, xi, 204). This short interval probably explains why the sino-auricular node normally gives no expression on the electrocardiogram separate from the activity ("P" wave) of the auricle. Under certain conditions in which the interval of sino-auricular conduction is probably delayed, the "P" wave of the electro-

which has as yet been applied clinically or experimentally is the absence of certain auricular beats in an otherwise regular auricular rhythm. The failure of the auricle to contract at such times may be due, as Hewlett[8] has pointed out, to (1) weakness of its muscle, (2) inadequacy of the stimulus, (3) blocking of the impulse between its point of origin and the auricle. Since in the cases which have been observed the curves show no evidence of any noteworthy variations in the size of auricular beats when these are present, the probability of variations in the strength of the excitation or in the responsive power of the muscle, of sufficient magnitude to account for a complete absence of contraction, would seem to be extremely improbable. That blocking of the stimulus is the true explanation is furthermore rendered probable by certain characteristics which the rhythm presents in common with auriculoventricular block. Of these the most significant are the facts that the intervals between the auricular beats immediately following the intermission is somewhat greater than in subsequent cycles and that the long cycles are nearly always somewhat less than twice the length of the short cycles. In the case of auriculoventricular block the latter feature finds its explanation in the fact that the period of auriculoventricular conduction is unusually long immediately before and unusually short immediately after the blocked cycles.

Several other authors have described cases of supposed sino-auricular block, the diagnosis of which was based on the character of the arterial pulse as counted or recorded. The extreme difficulty of excluding auriculoventricular block or extrasystolic arrhythmia in the absence of venous pulse or electrocardiographic records renders the interpretation in these cases open to serious question. Heincke, Abert, Mueller and von Hoesslin[8] described a case in which the arrhythmia suggested disturbances in sino-auricular conduction without actual block, and a second case in which the radial pulse suggested a partial sino-auricular block. Riebold[9] described two cases which showed changes in pulse rate suggesting sino-auricular block. In one of these the pulse was very slow and no visible jugular pulsations occurred

---

cardiogram may show a partial division into two waves, as has been described by Hering (Arch. f. d. ges. Physiol., 1912, cxliv, 1) and Eyster and Meek (see above). Probably the first wave in this case is a true measure of the activity of the seat of impulse formation. Many facts tend to support the view that the sino-auricular node normally does not show any or at best only an exceedingly small contraction. It is in this region where automaticity and conductivity are most developed, probably at the expense of contractility. The first movement of sufficient magnitude to affect the venous pulse does not occur until the right auricle enters into contraction. (Eyster: Jour. Exper. Med., 1910, xii, 257) and Eyster and Meek (see above.)

8. Heincke, Albert, Mueller and Höslin: Deutsch. Arch. f. klin. Med., 1908, xciii, 459.

9. Riebold: Ztschr. f. klin. Med., 1911, lxxiii, 1.

during the long pauses. Von Hoesslin[10] produced vagus pressure in a cardiac case and obtained dropped radial beats which he interpreted as sino-auricular block.

Hering[11] in 1901 described the first instance of supposed sino-auricular block obtained experimentally in animals. He observed the exposed hearts of rabbits and dogs dying from asphyxia and described varying degrees of partial block between the mouths of the superior vena cava and the right auricle. Similar observations were later recorded by Hirschfelder and Eyster.[12] Since it is now known that the heart beat normally arises not in the superior vena cava but in the sino-auricular node, and since it has been shown that dying hearts

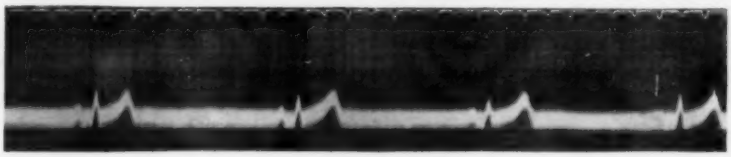


Fig. 1.—Interpreted as 2:1 sino-auricular heart block. The auricular cycles average 1.83 seconds. Figures 1 and 2 were made with Lead I (right and left hands). Figures 3, 4, 6, 7, 8, and 9 are electrocardiograms made with Lead II (right hand and left leg). All records are to be read from left to right. The time records in each case record fifth-second intervals.

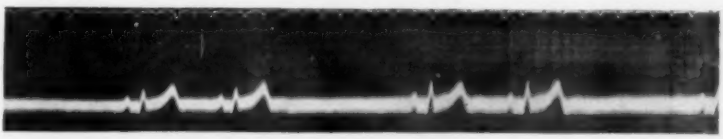


Fig. 2.—Interpreted as 3:2 sino-auricular block. The long cycles average 2.13 seconds, the short cycles 1.03 seconds.

may show initial contractions in regions which were not normally nor even at the time the seat of impulse initiation (Eyster and Meek[13]), these observations would seem to have little significance. Hering[14] later denied that sino-auricular block could exist in the mammalian heart because of the absence of a separate and independent sinus venosus. In 1906, however, he[15] described two cases of apparent sino-auricular block, one in a rabbit, the other in a dog, occurring without

10. Von Hoesslin: Deutsch. Arch. f. klin., Med., 1914, cxiii, 537.
11. Hering: Arch. f. d. ges. Physiol., 1901, lxxxvi, 553.
12. Hirschfelder and Eyster: Am. Jour. Physiol., 1907, xviii, 222.
13. Eyster and Meek: Heart, 1914, v, 137.
14. Hering: Ztschr. f. exper. Path. u. Therap., 1906, iii, 511.
15. Hering: Ztschr. f. exper. Path. u. Therap., 1906, iii, 511.

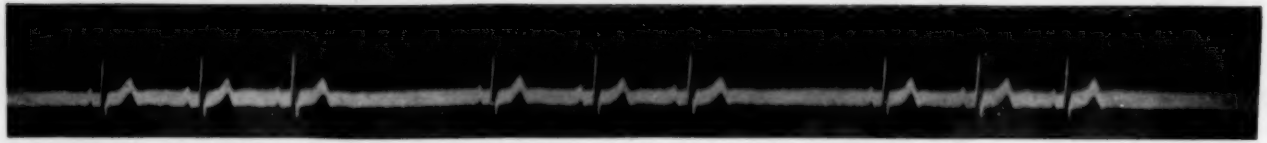


Fig. 3.—Interpreted at 4 : 3 sino-auricular block. The long cycles average 2.09 seconds, the short cycles 1.37 seconds.

known cause during the course of experiments carried out with other purposes in view. The criterion of diagnosis was the same as in the previously reported clinical case of Mackenzie.[1] Hering found that the suspension curves of the right auricle of the exposed heart showed occasional dropped beats in an otherwise regular rhythm. In 1907, Erlanger and Blackman[16] described sino-auricular block in excised and artificially perfused rabbits' hearts, resulting apparently from mechanical disturbance (traction) of the region of the sino-auricular node.

Fig. 4.—Showing alternating periods of sinus rhythm and auriculoventricular rhythm.

The criterion for diagnosis was the same as in Hering's experiments, dropped beats in the auricular suspension curve. In one the very slow rate of beat (less than 60 per minute) and the short As-Vs intervals (apparently less than 0.05 second) suggest an auriculoventricular rhythm in which the seat of impulse formation is in the auriculoventricular node at the base of the interauricular septum. In the other example the alternation in the size of the auricular beats suggests the regular occurrence of auricular extrasystoles, an extrasystole following each normal beat and followed by a compensatory pause. Erlanger

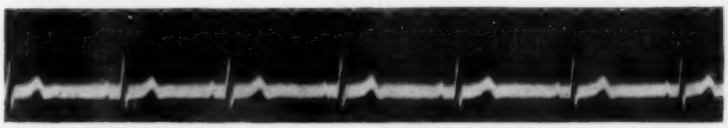


Fig. 5.—Interpreted as a normal rhythm. Auricular cycles average 1.17 seconds in length.

and Blackman were able to obtain the results described in two of six experiments in which traction was made on the sino-auricular node.

Cushny[17] in studying the effect of aconitin on the dog's heart *in situ* noted that not infrequently there was a sudden doubling or halving of the auricular rate and concluded that the condition was the result of the disappearance or appearance of sino-auricular block. Auriculo-

16. Erlanger and Blackman: Am. Jour. Physiol., 1907, xix, 125.
17. Cushny: Heart, 1910, i, 1.

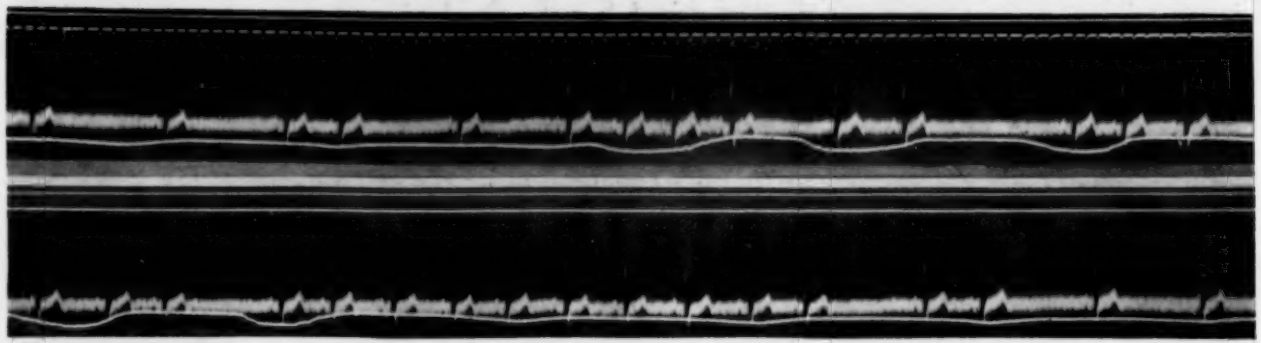


Fig. 6.—Shows transitory abolition of 2:1 and 3:2 sino-auricular block by deep breathing. The lowest line of the records shows the respiratory movements, downstroke representing inspiration. The lower record is a direct continuation of the upper and shows the return of block as the respiratory movements become of normal depth.

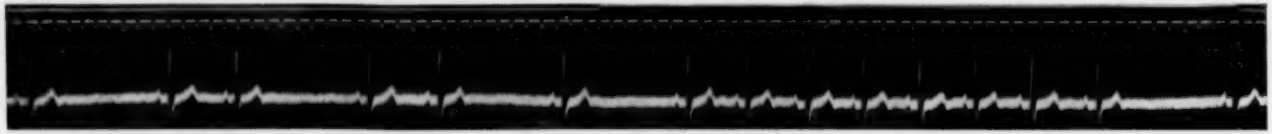


Fig. 7.—Shows transitory abolition of a 3:2 and 2:1 sino-auricular block by a series of swallowing movements (signalled by line at top of record).

ventricular block, partial or complete, was a very common result of aconitin administration in these experiments.

Eyster and Meek,[18] in 1913, investigated the arrhythmia in dogs that follows the administration of large doses of morphin, and concluded from electrocardiographic curves that the cause was a sino-auricular block alone or combined at other times with auriculoventricular block. Large doses of morphin (up to 2 grams) caused a slow regular heart rate which showed arrhythmia during its development or during the stage of recovery from the drug. The condition of slow regular pulse could be removed temporarily at any time by the injection of atropin, and in the change to a fast regular rate of approximately twice or three times the slow rate, marked arrhythmia was present. The results led to the conclusion that the slow regular beat

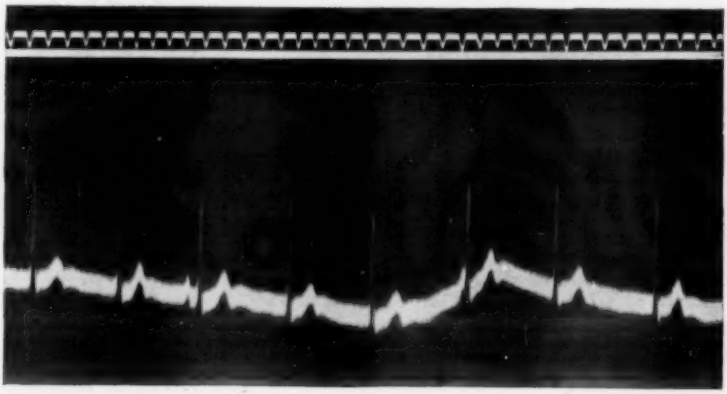


Fig. 8.—Period of auriculoventricular or "nodal" rhythm following exercise in sitting posture.

was a partial sino-auricular block of a regular nature in which, as a rule, every other or two successive sinus impulses were blocked. During the recovery from this slow rhythm, occurring spontaneously as a result of a wearing away of the morphin or resulting from its antagonism by atropin, various stages of partial sino-auricular and auriculoventricular block occurred. That morphin produces the slowing and arrhythmia of the heart by its action on the vagus mechanism, had been previously shown by von Egmond[19] and more recently by Einthoven and Wieringa[20] and by Cohn.[21]

18. Eyster and Meek: Heart, 1912, iv, 59.
19. Von Egmond: Arch. f. exper. Path. u. Therap., 1911, lxv, 197.
20. Einthoven and Wieringa: Arch. f. d. ges. Physiol., 1913, cxlix, 48.
21. Cohn: Jour. Exper. Med., 1913, xviii, 715.

REPORT OF A CLINICAL CASE OF SINO-AURICULAR BLOCK

J. O. R., a university instructor, aged 31, requested examination at the medical clinic because of slow irregular heart. He had been the subject of rather frequent examinations and states that his heart has been slow since early in life when his attention was first called to it by his family physician. He has recently been refused life insurance because of the slow heart rate. Family history is negative. Personal history negative except a severe attack of diphtheria at 2 years of age. Health good except occasional attacks of headache of migraine nature. Physical examination shows a fairly well-nourished man, height 5 feet, 9¾ inches, weight 143 pounds, and is entirely negative except for a moderate degree of extension of cardiac dulness to the left. No dulness to the right of the sternum. Heart sounds are clear. Pulse irregular, varies at different times from 36 to 60 beats per minute. Blood pressure (auscultatory method) in erect position 110 mm. systolic, 75 mm. diastolic. Urine negative except an occasional hyaline cast. Roentgenogram shows moderate degree of enlargement of the heart mainly involving the left ventricle.

The subject was examined by the aid of the electrocardiograph and jugular pulse tracings during seven periods of examination extending over ten weeks. Examination of the numerous records made during this time show that the longest heart cycle recorded was of 2.2 seconds duration, the shortest, except after exercise, 0.87 second. The heart cycles fall with remarkable constancy into two groups, the long cycles averaging about two seconds and the short cycles averaging about one second in length. In rare instances cycle lengths of the long variety as low as 1.6 seconds and short cycles as long as 1.2 seconds were observed. A regular succession of long cycles, a condition observed on several occasions, gave a slow regular heart rate of about thirty beats per minute (Fig. 1). A regular succession of short cycles gave a regular heart rate of approximately double this rate. A condition much more frequently met in the records is a rate intermediate between these, usually from thirty-six to forty-eight beats per minute and which is always arrhythmic. This may assume a number of different forms, depending primarily on the presence or absence of a definite relation between the short and long cycles. The relation between the two may be such as to give a bigeminal (Fig. 2) or trigeminal pulse (Fig. 3); two or three short cycles alternating with one long cycle with perfect regularity over long periods of time. Or the number in each group of short cycles may be much greater and markedly variable; varying from time to time from two to ten or more and frequently interspersed with several long cycles in succession. Finally there may be only an occasional long cycle interposed in a regular series of short cycles and the heart rate approaches the regular fast rate described above.

The long cycles are in nearly all instances approximately double the length of the short cycles, and neither the electrocardiogram nor the venous pulse show any movement during the former which could be interpreted as an auricular beat, the excitation from which is blocked before reaching the ventricle. The absence of "P" waves on the electrocardiogram and of "a" waves on the venous pulse during the long pauses make impossible the interpretation of the condition as auriculoventricular block. We are evidently dealing with a case of "dropped auricular beats in an otherwise regular auricular rhythm," pointing clearly to the interpretation of sino-auricular heart block. It would seem probable that the slow regular rhythm at the rate of about thirty beats per minute is to be interpreted as a regular 2:1 partial sino-auricular block, while the fast regular rhythm at approximately double this rate represents an entirely normal heart beat without interruption in the passage of any excitation from its points of origin to the remainder of the heart. The intermediate rates of beat, which, as noted above, are always arrhythmic, represent varying degrees of partial sino-auricular block. The arrhythmias show certain characteristics which have been noted in the cases of sino-auricular block previously described. The length of

the long cycles is usually slightly less than twice that of the associated short cycles, and the first cycle of each group of short cycles is usually somewhat longer than the remainder.

The rate of discharge of impulses from the sino-auricular node, according to the above interpretation, is under usual conditions approximately 60 per minute and is remarkably uniform throughout our observations. The records show no single instance which could be interpreted as representing the blocking of more than one sinus impulse in succession. The longest cycle recorded was 2.2 seconds. The condition would seem to be represented therefore by a series beginning with a 2:1 partial and regular block, passing through 3:2, 4:3, 5:4 regular partial block, irregular partial block varying from 2:1 to only occasional blocked impulses, and finally a 1:1 normal and regular heart beat.

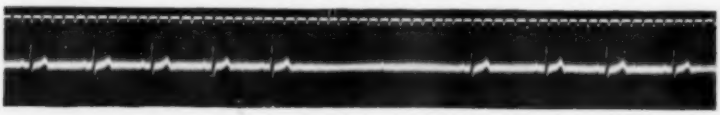


Fig. 9.—Influence of mechanical pressure on the right vagus nerve.

The case would seem to present certain points of unique character which are worthy of comment. The presence of this condition in an active man who is apparently in good health has its only precedent in the case described by Wenckebach.[3] It is the only case of sino-auricular block, so far as we can find, which has been entirely unassociated with auriculoventricular block. The only blocked auricular beats present in our observations occurred during experimental stimulation of the right vagus nerve by compression in the neck as described below. The regular character of the block present at various times on the one hand, and the ease with which the type of block could be varied by relatively slight disturbances (muscular movement, mental distur-

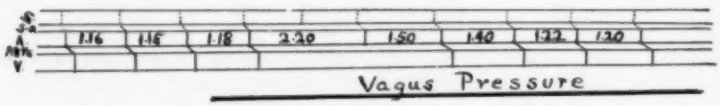


Fig. 10.—Schematic reproduction of record shown in Figure 9.

bance) on the other hand, are features not emphasized in the previously reported cases. Another interesting and unique feature in this case is the occasional occurrence of an auriculoventricular or "nodal rhythm." When in this condition, the electrocardiogram shows a regular succession of cycles with "P" waves fused with or preceding the "R" waves by an abnormally short interval. The change from a condition of sino-auricular block to that of auriculoventricular rhythm was noted in several instances on changing from the lying to the sitting posture. In one instance this change was produced by muscular exercise in the sitting posture. The cycles in auriculoven-

tricular rhythm are longer than the unblocked cycles in the sinus rhythm. The result of the change from sino-auricular block to auriculoventricular rhythm was usually, however, an increase in heart rate per minute. In a few records short periods of auriculoventricular rhythm alternated with periods of sino-auricular rhythm (Fig. 4).

In the attempt to find the reason for the existence of this condition in an apparently healthy man without evidence of other cardiac affection, consideration of the ease with which the type of block could be varied by relatively small external changes, of the influence of digitalis in the production of sino-auricular block in the previously reported cases, and especially the experimental production of sino-auricular block in dogs by morphin, led us to investigate the influence of the vagus nerves. That the condition was one easily influenced as to its character was evident from the readiness with which the rate and

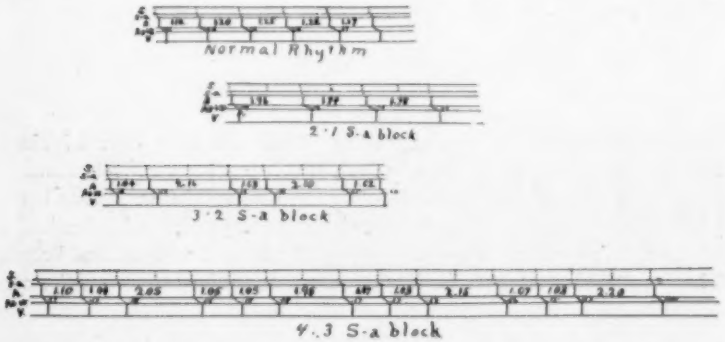



Fig. 11.—Schematic reconstruction of curves showing normal rhythm and 2:1, 3:2, and 4:3 sino-auricular block.

character of the beat changed. Sitting or lying quietly the heart would frequently fall into the slow regular rhythm of approximately 30 beats per minute, while slight muscular movement or disturbance of the quietness of the surroundings would lead to the characteristic arrhythmic faster rates, frequently showing groups of six to ten or even more successive short cycles. Experimentally it is evident that decrease in vagus tone is largely responsible for the moderate changes in heart rate resulting from muscular activity (Gasser and Meek[22]), and the changeable character of the beat in the present case suggested some such factor rather than an actual lesion within the conductive system, which would be expected to exert a more constant influence and tend to keep the character of the beat more nearly the same under fairly similar conditions.

22. Gasser and Meek: Am Jour. Physiol., 1914, xxxiv, 48.

The experimental observations that we have made indicate that the vagi are at least in part responsible for the sino-auricular block in this case. The subcutaneous administration of 1.0 mg. of atropin completely abolished the block for a time and led to the production of a regular heart rate of approximately 60 beats per minute. Figure 3 shows a trigeminal pulse present immediately before the administration of atropin, Figure 5, the regular beat present nine minutes following the injection. Other records showed that the trigeminal pulse passed, within four minutes following the administration, into a faster rate with only occasional dropped beats. A little later the rhythm became entirely regular at approximately 60 beats per minute, which condition lasted up to eighteen minutes after the injection, when occasional dropped beats were again observed. Within a half hour the condition had returned to practically that present before the atropin administration.

It is well known that normally the heart rate increases during inspiration, due largely at least to inhibition of vagus tone. Respiratory records made simultaneously with the electrocardiogram indicated

Fig. 12.—Carotid and jugular tracings showing 4 : 3 sino-auricular block. The absence of "A" waves in the long cycles excludes auriculoventricular block.

no change in the more regular types of block, such as the 3 : 2 and 4 : 3 rhythms, corresponding to the respiratory phase. At times when the type of block was irregular, when groups of short cycles of varying number alternated with long cycles, some relation to the respiratory phases was apparent. The long cycles were nearly always associated with expiration, and inspiration usually, but not always, called forth a group of short cycles. Rapid and deep breathing movements usually abolished the block and called forth a long uninterrupted series of short cycles (Fig. 6).

A succession of swallowing movements, a procedure which normally usually leads to a quickened pulse presumably due to diminished vagus tone, was found temporarily to abolish the existing block and to lead to the production of a regular fast rate of beat (Fig. 7).

The effect of muscular exercise was usually to remove an existing sino-auricular block and to accelerate slightly the rate of discharge

of the sino-auricular node. In one instance the cycle lengths in the unblocked cycles averaged 0.98 second before and 0.8 second immediately after the exercise. Arm exercise in the sitting posture in another instance converted a sinus rhythm with short cycle lengths of about 0.93 second and with a 3:2 and 4:3 sino-auricular block, into an auriculoventricular rhythm with cycle lengths of 0.82 second (Fig. 8).

Fig. 13.—Carotid and jugular tracing showing transition from 2:1 sino-auricular block to a normal rhythm.

Pressure on the right vagus nerve in the neck may cause the block to appear when not previously present (Figs. 9 and 10). Pressure on the left vagus produced merely a slowing of the sinus rate without evidence of block. In the curve reproduced, the sino-auricular block is combined with one blocked auricular beat, the only instance of auriculoventricular block in any of the records obtained.

The experimental results seem to us to point strongly to the vagus mechanism as at least in part responsible for the condition of sino-

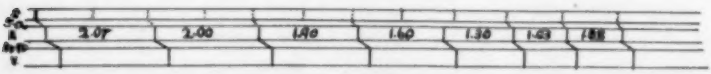


Fig. 14.—Schematic reproduction of record reproduced in Figure 13, showing probable interpretation.

auricular block in this subject. These factors which are known to inhibit vagus tone (atropin, inspiration, swallowing, exercise), tended to cause a disappearance of the block, while increase of tone of the right vagus produced by mechanical pressure on this nerve may cause the block to appear when not previously present. From the clinical standpoint there is no other apparent factor. The heart, except for the arrhythmia and slow rate and a moderate degree of ventricular

hypertrophy,[23] and the vascular system, are normal. In the absence of any apparent factor other than the vagus mechanism, we are inclined to attribute the condition in this case to an abnormal vagus tone. The influence of the vagus on the conductivity in the heart is evident from the experiments of many investigators on the lower animals and from the work of Ritchie[24] and of Robinson and Draper[25] on the results of vagus pressure in man.

SUMMARY

In a case of sino-auricular heart block occurring in a man, 31 years of age, who is in apparently good health and clinically normal with the exception of the block and a moderate degree of cardiac hypertrophy, diagnosis of the condition was made by the aid of the electrocardiogram and venous pulse tracings. It has persisted under observations for ten weeks and from the history has probably been present for years. The type of block varies from a 2:1 partial sino-auricular block to only occasional blocking of systoles. At times an auriculoventricular or nodal rhythm was observed, present alone or combined with sinus block. Occasionally a normal cardiac rhythm was present. The block was found to be abolished by atropin, by deep rapid breathing, by swallowing movements, by exercise, and to be brought on or increased by pressure on the right vagus nerve in the cervical region. It is suggested that the condition results from an abnormal vagus tone. It was unassociated with auriculoventricular block. The rate of beat varies at different times from approximately 30 to 60 beats per minute, and shows a slow regular rhythm and a fast regular rhythm. The intermediate rates are always arrhythmic, due to the dropping of systoles in an otherwise regular rhythm. The slow regular rate is interpreted as a 2:1 sino-auricular block. The fast regular beat is due to a normal rhythm without block. In addition there was at times a somewhat slower regular rate of auriculoventricular or "nodal" origin.

23. The cardiac shadow area as measured by the method of Dietlen is 143.5 sq. cm. The normal for a man of the patient's weight, according to Dietlen is about 120 sq. cm. A sufficient explanation for the presence of the hypertrophy would seem to be present in the very slow heart rate that has apparently been present for many years. With a heart beating at from one-half to two-thirds the usual rate and yet maintaining a normal blood pressure, each beat must be correspondingly larger; a condition which in time would certainly lead to hypertrophy.

24. Ritchie: Quart. Jour. Med., 1912-1913, vi, 47.

25. Robinson and Draper: Jour. Exper. Med., 1911, xiv, 217.

CLINICAL STUDIES ON THE RESPIRATION. NO. 1

THE EFFECT OF CARBON DIOXID IN THE INSPIRED AIR ON PATIENTS WITH CARDIAC DISEASE *

FRANCIS W. PEABODY, M.D.
BOSTON

Recent physiologic investigations have shown conclusively that the most important factor controlling the respiration is the reaction of the blood. Through the agency of the kidneys, which excrete non-volatile acids, and the lungs, which excrete volatile acids, the hydrogen ion concentration of the blood is kept within the narrow limits which are compatible with life. A rise of the acidity of the blood above its normal level stimulates the respiratory center and increases pulmonary ventilation to such an extent that the tension of carbon dioxid is reduced and the normal reaction of the blood is upheld. Anything which causes an increase in the carbon dioxid tension of the blood results in an augmented ventilation of the lungs. Hence the dyspnea after moderate exercise, and the dyspnea produced by breathing an atmosphere containing high percentages of carbon dioxid. In the studies to be described in the present paper the fact that carbon dioxid acts as a stimulus to the respiration forms the basis of its use as a functional test. Subjects have been allowed to breathe air in which the amount of carbon dioxid was constantly rising, and their ventilation has been measured. Thus the effect which known percentages of carbon dioxid produced on the respiration could be readily determined, and curves could be plotted showing the increase in ventilation resulting from the rise of carbon dioxid in the inspired air.

The effect of carbon dioxid was first studied in a number of normal individuals of different ages and weights, and it was found that within rather narrow limits a given increase in the percentage of carbon dioxid in the inspired air produced a definite increase in the pulmonary ventilation. Thus a curve of the normal response to the stimulus could be established. Similar investigations were then made on pathologic patients in whom dyspnea had been a prominent factor. The cases here reported fall into two groups, those of pure cardiac disease, and those which are best described by the term "cardiorenal" disease. Since pathologic conditions underlying the dyspnea in these two classes of cases are apparently somewhat different, it is proper that the groups should be considered separately.

* Submitted for publication June 23, 1915.
* From the Medical Clinic of the Peter Bent Brigham Hospital.

The use of carbon dioxid in the inspired air as a means of producing dyspnea in a functional test of the respiration has certain advantages. It is a comparatively simple method and affords ready and accurate determination of the amount both of stimulus and response. Furthermore, it gives a relatively uncomplicated picture of the results produced by a single factor. If, for instance, exercise is used as a means of producing dyspnea, the results are confused because the development of skeletal muscles, training, degree of adiposity, and the functional capacity of the heart all play important parts in determining the degree of dyspnea produced by a given amount of exercise. In using carbon dioxid in the inspired air as a test of respiration the stimulus can be graded, and a comparatively large effect on the ventilation may be obtained with a minimum of discomfort to the patient. As the test can be made with the patient lying quietly in bed, it may be safely applied to patients whom it would not be proper to move.

Two general methods were applicable. On the one hand one might give the subject air to breathe containing a fixed and known amount of carbon dioxid. Such a method was used by Lindhard[1] in his studies on the excitability of the respiratory center. Or it would be possible to use the "closed-circuit" method, in which the patient would rebreathe his own inspired air and would thus himself produce the carbon dioxid which should serve as the stimulus to respiration. This method was used by Hough,[2] but in his experiments no systematic analyses of the inspired air are recorded, so that they have a very indirect bearing on the present work.

THE METHOD

The subjects, sitting on a chair, or propped up in bed, breathe through valves which separate the inspired from the expired air, into a closed system. The valves are of glass with rubber flaps, of a form designed by Krogh. Respiration is through the mouth, the nose being tightly closed by a clip. The expired air passes into a large tin box holding about 27 liters. The expired air enters the box at the top and leaves by an outlet tube near the bottom, thus having ample opportunity for the diffusion of gases. Leaving by the outlet tube the air passes to a second tin box, similar in size and construction to the first and again allowing thorough mixing. From the lower part of this second box an outlet tube runs to the inspiratory valves. A small tube is inserted in the side of this second box through which samples of air may be taken for the determination of the composition of the inspired air. A short side tube, leading off from the tube connecting the two

1. Lindhard: Jour. of Physiol., 1911, xlii, 337.
2. Hough: Am. Jour. Physiol., 1911, xxviii, 369.

tin boxes, runs to a small Krogh volumetric spirometer. The movements of the spirometer are recorded on the smoked paper of a kymograph, and by means of a calibrated scale the volume of each respiration can be accurately measured. A timer marking five-second intervals was used. The whole apparatus, with the exception of the valves and tubing leading to and from the tin boxes, was concealed by a screen, so that the subject's attention should not be distracted by the moving spirometer and kymograph.

In most instances a pneumographic record of the respiration was taken while the subject was at rest, and before breathing through the valves was begun. This gave the normal rate and some information as to the character of the respiration, but was of little value in giving evidence as to the depth of respiration. In other cases the respiration at rest was counted. The pulse rate at rest was also counted. The rubber mouthpiece was then put into the subject's mouth, connected with the valves, the nose clip put in place and the experiment started. A continuous record of the respiration was kept on the kymograph. Every two minutes a sample of inspired air was taken, and at the same time the pulse was counted. The experiment was continued until a degree of dyspnea was produced which caused discomfort or distress to the subject. As will be seen below, the length of the experiment depended on a number of factors and was variable. At the end of the experiment the samples of inspired air were analyzed. In all the earlier experiments both oxygen and carbon dioxid were determined, but as the oxygen fell to a degree that was quite parallel to the rise of carbon dioxid, and as the oxygen rarely got so low as to be a significant factor in the production of the dyspnea, the analysis of samples from the later experiments was usually limited to the determination of carbon dioxid. In all cases, however, in which the carbon dioxid in the inspired air had risen especially high, the oxygen was also determined. With an adult of average size the carbon dioxid concentration reached 6 per cent. in about fifteen minutes, and at this time the oxygen would have dropped to approximately 13 per cent. In one unusual experiment the subject continued breathing until the carbon dioxid had risen to 9.06 per cent., and the oxygen had fallen to 8.96 per cent. From the kymographic record of the respiration the rate, volume per respiration, and the total ventilation per minute were calculated. When the respiration was regular the total ventilation was determined by multiplying the rate by the volume of a single respiration, but when it was irregular the volume of each respiration during a minute was measured. The percentage of carbon dioxid in the inspired air was then compared with the total ventilation during one minute. The minute over which the total ventilation was measured was so

chosen as to end just after the sample of air was taken. The relation between the total ventilation and the carbon dioxid in the inspired air is best shown graphically by means of a chart on which the abscissae represent the percentage of carbon dioxid in the inspired air, and the ordinates show the percentage increase in the total ventilation. The total ventilation during the second minute was in most cases (see below) assumed to be the resting value, and charted on the base line (100). The ventilation of subsequent minutes is charted in terms of percentage increase of this figure. The figure representing the percentage increase has been termed the ventilation coefficient. Thus when the ventilation doubled its initial value, the coefficient is 200. A coefficient of 300 signifies a ventilation which is three times the resting amount. A curve may thus be plotted which will show the increase of ventilation corresponding to the increase of carbon dioxid in the inspired air.

There are various limitations and sources of error in an experimental procedure such as that outlined. It would undoubtedly be better to study the effect of increasing carbon dioxid on alveolar ventilation rather than on total ventilation, since the alveolar ventilation is the important factor to the organism. Lindhard[1] has made this point clear in his work on the excitability of the respiratory center. The determination of alveolar ventilation, however, requires a knowledge of the size of the dead space, and at present when both the methods of determining the dead space and the possibility of there being considerable variation in the size of the dead space under physiologic and pathologic conditions are being actively debated, it seemed wiser to study only the total ventilation. Determinations of the dead space in some patients would have been a very difficult problem.

Another point which makes for inaccuracy in the curves is the fact that the air analysis represents the composition of the inspired air at only one particular instant of the minute over which the ventilation was being measured. This is not especially important, however, as the system was so large that the percentage of carbon dioxid rose rather slowly. Of more significance are the errors which depend on making an untrained subject breathe through the mouth. Frequently the character of the respiration is changed from the normal, usually in the direction of somewhat slower and deeper breathing. Subsequent questioning often brought out the fact that the subject was wholly unaware of this change, and after the first few breaths felt no discomfort from mouth breathing. It seems probable that although the character of the breathing was altered, the alveolar ventilation remained practically unchanged. There was usually only slight change in the total ventilation during the first five minutes of the experiment, as the carbon

dioxid in the inspired air was but little over 1 per cent. The rise in the ventilation in this period was rarely more than 10 to 15 per cent. over that during the second minute. The value during the second minute was usually assumed to be the "initial ventilation," and at this

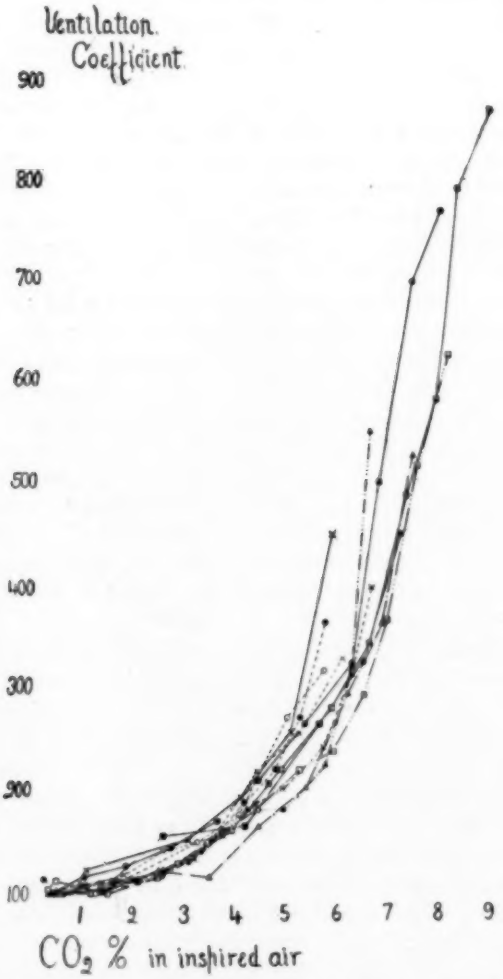


Fig. 1.—Ordinates: percentage increase in minute volume of ventilation. Abscissae: percentage increase in carbon dioxid content of inspired air. The curves show the response of a series of normal subjects to increasing amounts of carbon dioxid. The ventilation is doubled when the inspired air contains 4.3 to 5.4 per cent. carbon dioxid.

time the carbon dioxid was not often over 0.3 per cent. In some instances the ventilation in the fourth minute was less than in the second, due apparently to the fact that the subject took longer to get accustomed to the apparatus. Under these circumstances the later and lower ventilation is charted as the resting value (100). Another factor which tends to diminsh the absolute accuracy of the records is the slight irregularity of the response of an individual subject to the same stimulus on different occasions. In two or more experiments on the

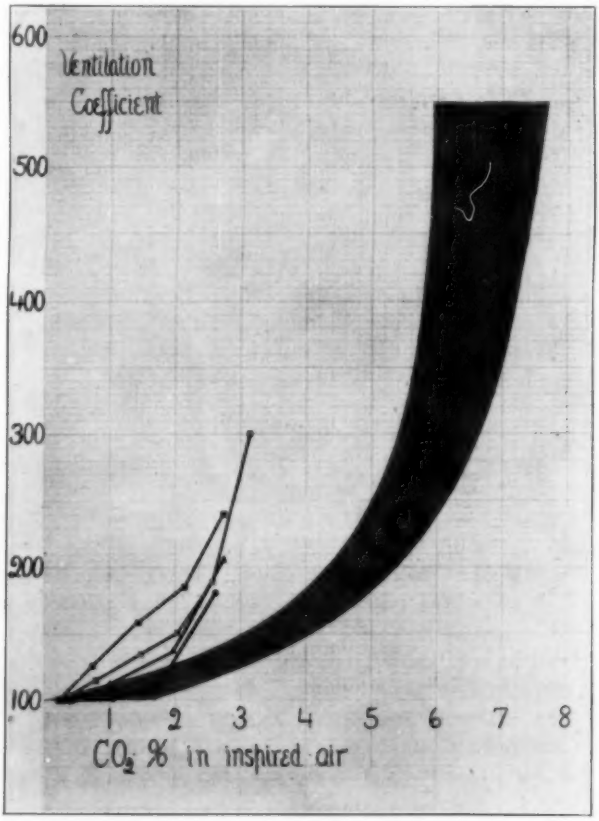


Fig. 2.—Ordinates: percentage increase in minute volume of ventilation. Abscissae: percentage increase in carbon dioxid content of inspired air. The shaded curve shows the response of normal subjects to increasing amounts of carbon dioxid. The ventilation is doubled when the inspired air contains 4.3 to 5.4 per cent. carbon dioxid. The black lines show the response of patients with acidosis. The ventilation is doubled when the inspired air contains only 2 to 3 per cent. carbon dioxid.

same subject the points on the curve are rarely exactly superimposed, owing probably to varying psychic and metabolic conditions. However, perhaps the most striking feature which has come out of the observations on normal individuals is the fact that in spite of these chances for error and inaccuracy there is a very definite curve of response which will serve as a normal, and may be used for comparison with pathologic conditions.

NORMAL SUBJECTS

The normal subjects on whom observations were made represent various sizes and types. Several were young men who had been athletes, and were in good training at the time of the experiments. Among the others were medical students and physicians accustomed to little exercise and rather easily winded. One subject was a young man in first-class training weighing 205 pounds, while another was a slim girl of 14 whose weight was 98 pounds. The rest fell in between these extremes. The experiments revealed no differences in the reaction to carbon dioxid which bore any relation to age, size, or weight.

Chart 1 shows the curves representing the response of nine normal individuals to increasing amounts of carbon dioxid in the inspired air. It will be noted that in spite of the variations of single points, and of the differences in individuals, all the curves follow the same general line. There is at first a very slow increase in ventilation. By the time the carbon dioxid has reached between 3 and 4 per cent., the ventilation is in most cases one half again as great as normal. Then follows a sharper rise of the curve so that when the carbon dioxid is between 4.2 and 5.4 per cent. the total ventilation has doubled. Beyond this point greater individual variations begin to show themselves, and small increases in the carbon dioxid cause much greater increase in the total ventilation. Above the line marked 300, the point at which the ventilation has been trebled, the chart is of less significance from the point of view of the present study, but certain facts of interest may be brought out. In performing the experiments it was intended that the subjects should continue until dyspnea became uncomfortable or until they became slightly dizzy. The majority continued breathing until the inspired air contained from 5.5 to 7 per cent. carbon dioxid. Those who were able to go on until they were breathing air containing from 7.5 to 9 per cent. carbon dioxid were all individuals who were capable of producing an extremely large ventilation, and as it happened, were the men who had been most athletic and were in the best training. K. L. D., who breathed the highest percentage of carbon dioxid and whose ventilation became more than eight times the normal, was the largest subject, and probably the most highly trained. F. G. B., who went easily to 8.2 per cent. carbon dioxid, and whose

ventilation was above six times the normal, is medium sized. On the other hand, E. H., the girl mentioned above, was able to breathe a mixture containing 6.7 per cent. carbon dioxid without discomfort, her ventilation rising to nearly four times the normal. Both carbon dioxid and ventilation were in her case higher than in the experiments done with some of the men who were much larger and stronger. Thus no direct relationship exists between the age, size, or weight of a subject and the percentage of carbon dioxid which they can breathe. The percentage of carbon dioxid which can be breathed without discomfort seems to depend on the ability to increase the ventilation.

As in the experiments of Hough,[2] it was found that some persons increase their ventilation chiefly by increasing the rate, while others depend chiefly on increase in depth. The majority begin by increasing the volume of each inspiration, then later increase the rate, so that toward the end of the experiment both rate and depth are much above normal. The time of the experiment was very variable and depended on the rate at which carbon dioxid was produced by the subject. The average subject was breathing approximately 5 per cent. carbon dioxid at the end of about twelve minutes. K. L. D., a large individual, was breathing 9.06 per cent. carbon dioxid at the end of twenty-three minutes; while W. L. B., a small man, was breathing only 5.78 per cent. carbon dioxid after twenty-four minutes. Thus on account of variations in rate of production of carbon dioxid in persons of different size and of different metabolic activities, the time element is of no significance. Hough has already called attention to the fact that in order to get comparative curves the size of the closed system must be adapted to the size of the subject. In the present work this difficulty is avoided as the time element is neglected, and the carbon dioxid content in the inspired air is the factor compared with the ventilation.

Table 1 shows the chief data at the beginning and at the end of the experiments on normal individuals.

Pulse Rate.—The pulse rate was taken every two minutes during the experiment, at the same time at which samples of inspired air were taken for analysis. In general the pulse rate increases very slightly with the increase of respiration. By the time the ventilation was doubled the pulse rate had usually risen only 2 to 10 beats per minute. In several instances it was slower than at the beginning of the experiment. The pulse rate remained practically unchanged at the time at which the ventilation was trebled. With the ventilation quadrupled the pulse rate was rarely more than 10 beats per minute above its rate at rest. Only occasionally during the last two minutes, when the subject was pumping hard, would the pulse rate become as much as

TABLE 1.—Normal Subjects

Subject	Rate of Respiration		Single Respiration, c.c.		Total Ventilation per Minute, Liters		Ventilation Coefficient at End	Per Cent. CO_2 in Inspired Air at End
	Initial	Final	Initial	Final	Initial	Final		
F. G. B.	14	22	815	3,291	13.00	72.41	622	8.30
W. M. B.	22	22	352	1,268	8.82	27.90	300	5.78
D. W. C.	24	36	450	900	10.80	32.40	313	5.75
E. C. C.	12	22	822	2,346	9.86	51.61	324	7.52
E. C.	14	25	668	1,902	8.69	47.56	548	6.07
K. L. D.	10	20	695	2,668	6.95	53.37	767	8.06
	10	17	800	2,100	8.00	35.75	446	7.27
E. H.	21	78	350	1,038	7.35	29.05	395	6.70
F. W. P.	11.5	18	600	1,600	6.90	30.80	446	5.92
N. S. S.	14	19.5	600	1,400	8.40	27.30	325	6.12

20 beats per minute above normal. This brings out an interesting difference between dyspnea produced by breathing high percentage of carbon dioxid and the dyspnea caused by exercise. In the latter one would expect a much greater rise in pulse rate with a corresponding degree of dyspnea.

PATHOLOGIC CASES

The pathologic cases studied with the method just described are all instances of cardiac or of cardiorenal disease. It was hoped that some light would be thrown on the mechanism of the production of dyspnea in these conditions. There is a considerable body of evidence to show that different factors take part in causing dyspnea in these two groups of cases. In the pure cardiac cases the dyspnea seems to depend on a slow or insufficient circulation, which results in a poor oxygenation of the tissues, and may even cause a transient acidosis owing to the incomplete combustion of metabolic products. In the cardiorenal cases this may be complicated by the presence of a considerable permanent acidosis, depending on imperfect renal excretion. In the present paper these groups are therefore taken up separately. Moreover, in order to obtain as clear an understanding of the subject as possible, a further subdivision has been made, depending on whether or not the cardiac condition was "compensated" at the time of the experiment.

I. CARDIORENAL DISEASES

A. Decompensated Cases.—Four cases fall into this group, and on one of them observations were made on two occasions ten days apart. All of these patients showed slight, moderate or rather severe dyspnea.

A common characteristic of their respiration was its periodicity or tendency to be of the Cheyne-Stokes type. Periods of true apnea of over a few seconds duration were not seen at the time when the observations were made, and sometimes the periodicity was not noticed until pneumographic tracings were made. It usually became less evident after the patient began to breathe through the valves, and disappeared when the percentage of carbon dioxid in the inspired air began to rise. The disappearance of Cheyne-Stokes respiration under the influence of an increased concentration of carbon dioxid in the air breathed has frequently been observed before. The phthalein test showed an output for two hours of 15 per cent. for J. P. C., of 6.5 per cent. for J. W. O'M., and of 40.5 per cent. for D. N. The latter patient showed marked arteriosclerosis. All of these patients were in the terminal stage of their disease, although two of them were still living some weeks after the dates on which they were studied. From the point of view considered here, the most important and characteristic feature which these cases shared in common was the existence of an acidosis. This was shown by the low tension of the carbon dioxid in the alveolar air.

The initial ventilation varied from 9.5 to 15.99 liters, and was higher than would be expected in normal persons of the same size. Under the influence of carbon dioxid both the rate and the depth of respiration became increased, but the concentration of carbon dioxid which the patient could breathe was much below that tolerated by normal subjects. One patient was able to continue breathing until his ventilation was a little more than three times what it was at rest. It was necessary to stop the others when their ventilation was somewhat more than doubled or even before this. The total ventilation, when the observation was discontinued on account of dyspnea, was from 18.81 to 28.6 liters. With the normal subject the ventilation at the end was from 3.25 to 8.7 times as great as at the beginning and amounted to from 27.3 to 72.41 liters. Still more striking was the rate of the response. While the normal subjects doubled their ventilation when the carbon dioxid in the inspired air was approximately from 4.2 to 5.4 per cent., these patients increased their ventilation much quicker, and with a much lower percentage of carbon dioxid. In other words, they reacted to a lower stimulus. Table 2 shows the total ventilation, percentage of carbon dioxid in the inspired air and ventilation coefficient at the end of the observation, as well as the alveolar carbon dioxid tension in each case. The alveolar air was taken by the Plesch-Higgins method.[3]

3. Boothby and Peabody: THE ARCHIVES INT. MED., 1914, xiii, 497.

TABLE 2.—CARDIORENAL DISEASE; DECOMPENSATED CASES

Subject	Rate of Respiration		Single Respiration, c.c.		Total Ventilation per Minute, Liters		Ventilation Coefficient at End	Per Cent. CO_2 in Inspired Air at End	Alveolar CO_2 Tension, mm.
	Initial	Final	Initial	Final	Initial	Final			
J. P. C. ...	21.5	25	...	.....	16.37	18.81	181	2.62	34.5
C. J. D.	18	31	672	836	12.10	24.90	206	2.74	34.6
D. N.	14	26	600	1,100	9.52	28.60	300	3.14	29.2
	19	27	500	850	9.50	22.85	240	2.74	26.9
J. W. O'M.	20	32	516	841	15.99	26.52	172	3.69	36.1

J. W. O'M. would practically fall into the normal group as far as the rate of his response is concerned. He was, however, markedly dyspneic when he was breathing air containing 3.69 per cent. carbon dioxid, and could not readily increase his ventilation coefficient above 172. It is noteworthy that his is the highest alveolar carbon dioxid in the group.

Chart 2 shows graphically the response of these subjects. The shaded area indicates the normal field of response to the increasing carbon dioxid, and the lines illustrate the effect produced on some of the patients with acidosis.

Pulse.—Satisfactory pulse records were obtained in only three observations. With D. N. the pulse rose from 78 at rest to 108 when the ventilation coefficient became 334, and from 98 to about 117 when the ventilation coefficient was 240. The patient had auricular fibrillation. On this, and in all patients with auricular fibrillation, the heart rate was determined by auscultation at the apex, and not by palpation of the arterial pulse. The pulse rate of J. W. O'M. rose from 88 to 104 when the ventilation coefficient rose to 172. On the whole the pulse rate seemed to be slightly more affected than in the normal individuals, but when it is considered that both sets of patients were extremely dyspneic, the difference in pulse rate is very slight. The pulse rate varies with the degree of dyspnea. It is certain that muscular exercise sufficient to produce the amount of dyspnea which these patients exhibited would have caused a much greater rise in pulse rate.

B. Compensated Cases.—Four subjects, two of whom were also studied during a period of decompensation and have been considered in the last section, belong in this group. These were all cases of definite cardiorenal disease in whom the nephritis seemed to be the prominent factor. Dyspnea was not noticeable while the patients were at rest, but was easily produced by exertion. Pneumographic tracings brought out the fact that irregular respiration, with a tendency

to periodicity, was a common characteristic. It is important that the alveolar air examinations in all of these cases showed a normal carbon dioxid tension, thus demonstrating that no high grade of acidosis was present.

The subject P. C., the mildest case, had chronic nephritis with hypertension and high-grade emphysema. His phthalein output was normal. E. L. W. had a chronic nephritis with hypertension and a phthalein output of 36 per cent. He complained of considerable dyspnea on slight exertion. J. W. O'M. had chronic nephritis with hypertension and his phthalein excretion was 10 per cent. in two hours. He had marked dyspnea on exertion, and gave a history of severe sudden attacks of nocturnal dyspnea. He had such an attack the night before this observation was made. The patient gradually became worse and was studied again (as reported in the last section) a month later when he had begun to have dyspnea while at rest, and when his alveolar carbon dioxid tension had dropped below normal. Case J. P. C. was also reported on in the last section. He had a chronic nephritis with a phthalein output of 15 per cent. Strictly speaking, this case should probably be grouped among the decompensated cases, as there was no essential difference in his clinical condition at the times of the two observations. On both occasions he had orthopnea with irregular and periodic breathing. In order to test accurately the relation of the acidosis to the increased sensitiveness shown by the last group of cases to carbon dioxid, it was decided to attempt to overcome the acidosis in this patient by administering alkali. It was necessary to give 95 gm. sodium bicarbonate before the urine became alkaline. The alveolar air was then taken, and the carbon dioxid tension found to be 47.3 mm., somewhat above the usual normal limit. It is on account of the absence of acidosis that this observation was considered in the present group. It is a fact of considerable importance that although there was very little change in his general condition, the effect produced on his ventilation by carbon dioxid in the inspired air was now exactly similar to that produced in normal persons.

The observations on this group of cases show that their reaction to the increasing carbon dioxid in the inspired air is no more rapid than it is in the normals, in spite of the fact that they have a much greater tendency to dyspnea on exertion. The total ventilation did not become doubled until the carbon dioxid in the inspired air had reached approximately 4.5 per cent. The concentration of carbon dioxid which they could breathe without too intense dyspnea is below that which the normal controls could breathe. Both the total ventilation and the ventilation coefficient are distinctly below the normal average. J. C.

could have continued breathing longer, but as he was rather sick the observation was stopped as soon as dyspnea began. He said that he "felt a little short-winded but could have stood it a few minutes more." Table 3 shows the alveolar carbon dioxid tension as well as the essential data at the beginning and the end of the observations.

TABLE 3.—CARDIORENAL DISEASE; COMPENSATED CASES

Subject	Rate of Respiration		Single Respiration, c.c.		Total Ventilation per Minute, Liters		Ventilation Coefficient at End	Per Cent. CO_2 in Inspired Air at End	Alveolar CO_2 Tension, mm.
	Initial	Final	Initial	Final	Initial	Final			
P. C.	9	22	772	1,285	6.95	28.26	407	6.58	46.1
J. P. C.	17	23	...	.....	7.84	15.08	193	4.66	47.3
J. W. O'M.	15	26	...	.....	10.15	25.86	254	4.97	42.8
E. L. W. ...	14.5	14	550	1,200	7.98	16.80	210	4.42	45.1

Pulse.—The rise of pulse rate during the observation agrees well with what was seen in the normal subjects and was approximately from 10 to 20 per minute.

II. CARDIAC DISEASE

A. Decompensated Cases.—Four cases of valvular disease may be grouped under this heading. All of the patients showed orthopnea and a moderate amount of dyspnea even while they were at rest in bed. Three of these patients were studied twice on two successive days and will be considered together, as they had a low alveolar carbon dioxid tension, a feature which seems to be of considerable importance. The carbon dioxid tension varied from 30.9 to 37.7 millimeters. This moderate depression has been found to be present in many instances of pure cardiac dyspnea during the most acute stage. It passes away quickly as soon as the patient begins to get compensated. Cyanosis was not especially striking in any of the cases, but its presence was noted in two of the patients. Periodic respiration was observed in two cases. On the whole the effects produced by inspiration of air containing increased amounts of carbon dioxid were about the same as with the decompensated cardiorenal cases. It required less carbon dioxid to induce dyspnea than was needed with the normal subject. While the total ventilation is normally doubled by breathing air containing 4.2 to 5.4 per cent. carbon dioxid, in these patients it was doubled by air containing between 3 and 4 per cent. carbon dioxid. There is apparently a fairly close relationship between the alveolar air and the pulmonary response, in that the lower the alveolar carbon dioxid tension, the less the concentration of carbon

dioxid in the inspired air that is required to produce a given increase in the ventilation. The concentration of carbon dioxid which the patients could breathe was much lower than that which normal individuals are able to stand. The total ventilation at the end of the observation, when the dyspnea was at its height, was much less than the average normal, and the ventilation coefficients were far below the values with normal subjects. The figures for R. B. do not represent her maximum effort, as the experiment was stopped shortly after the onset of dyspnea in order not to fatigue her too much.

One case formed an exception to the above statements. M. M., with chronic valvular disease, was studied at a time when he had considerable dyspnea, although he was lying quietly in bed propped up on a back rest. He had only slight cyanosis. The alveolar carbon dioxid tension was 42.4 millimeters. He thus corresponds to the group of decompensated cardiac cases without acidosis, as described by Lewis. The experiment with this patient showed that he could breathe a much higher concentration of carbon dioxid (5.16 per cent.) than could those decompensated cases which had an acidosis. In spite of the fact that he was very dyspneic at the end of the observation, his total ventilation rose only from 12.65 to 20.8 liters, and the volume of the single respiration from an average of about 575 cubic centimeters to about 650 cubic centimeters. This patient differed again from the other decompensated cases in that his ventilation coefficient rose only to 165 when there was 5.16 per cent. carbon dioxid in the inspired air. Thus he did not show the sensitiveness to carbon dioxid which was characteristic of the other patients with dyspnea. Indeed, his ventilation increased less rapidly under the influence of the added stimulus than did that of the normal individuals.

TABLE 4.—Cardiac Diseases; Decompensated Cases

Subject	Rate of Respiration		Single Respiration, c.c.		Total Ventilation per Minute, Liters		Ventilation Coefficient at End	Per Cent. CO_2 in Inspired Air at End	Alveolar CO_2 Tension, mm.
	Initial	Final	Initial	Final	Initial	Final			
R. B.	24	31	300	450	7.71	14.44	187	3.43	35.2
J. H. B. ...	17	24	...	...	9.55	26.63	279	4.10	37.7
	18.5	24	...	...	11.58	25.96	219	3.70	34.3
W. M.	19.5	27	410	600	8.00	16.20	202	3.41	30.9
M. M.	22	32	575	650	12.65	20.80	165	5.16	42.4

Table 4 shows the alveolar carbon dioxid tensions and the various factors of importance at the beginning and the end of observations on the cardiac cases with decompensation.

Pulse.—The rise in pulse rate during the observation was not over 15 per minute in three cases. In W. M. the rate rose from 108 to 154 when his total ventilation doubled. This was a patient with auricular fibrillation. During one observation the pulse rate of J. B. rose from 86 to 100 per minute. After he was completely rested the effect of exercise was tried, by making him sit up and lie down in bed seven times. This pulse rate rose from 82 to 100 per minute, but his dyspnea was much less than it was in the carbon dioxid experiment.

B. Compensated Cases.—Ten patients with cardiac disease, valvular or myocardial, were examined at a stage when their hearts were so well compensated that they had no dyspnea while they were at rest in bed. In all of them dyspnea was easily produced by slight exertion. A total number of 17 experiments was performed on this group. Four of the patients had been previously studied during the period when they were decompensated and were having dyspnea even while at rest. In all the subjects of this group the alveolar carbon dioxid tension was normal, and there was no evidence of acidosis. The percentage of carbon dioxid in the inspired air which these patients were able to breathe was higher than that which the decompensated cardiac cases were able to take, but was not on the whole as high as the normals could breathe. As the dyspnea increased the size of the individual respirations increased, more so than with the decompensated patients, but in general less than with the normals. The total ventilation was also greater than in the decompensated group, but less than in the normal subjects. Although in considering this point it must be borne in mind that the sick patients were stopped before they became quite so breathless as the normal individuals were allowed to become, it appeared to be quite definite that the extent to which they were able to increase their pulmonary ventilation was distinctly limited. This is also brought out by comparing the ventilation coefficients of the two groups. The percentage increase of ventilation as shown by the ventilation coefficient rose, in its relation to the carbon dioxid of the inspired air, exactly as in the normal subjects. The ventilation became doubled when air containing between 4.2 and 5.4 per cent. carbon dioxid was being breathed. There was thus no hypersensitiveness to carbon dioxid as was manifested by the decompensated cases with acidosis. This is especially interesting when it is remembered that exercise would produce dyspnea in these patients very much more easily than in healthy persons, and again shows that the test employed here has quite a different influence on the respiration than has physical exercise.

Two cases proved to be exceptions to the above statements. W. E. M. was studied on two occasions over a week apart after his dyspnea had disappeared, and after his alveolar air had become nor-

mal. He could stand a higher percentage of carbon dioxid, and both his total ventilation and ventilation coefficient increased much more than before he became compensated, but he remained hypersensitive to carbon dioxid, and doubled his ventilation under the influence of 2 to 3 per cent. carbon dioxid. It is noteworthy that he was the sickest patient in this group. W. M., the patient who while still dyspneic had a normal alveolar carbon dioxid tension, showed a hyposensitiveness to carbon dioxid in that when he was breathing 5.32 per cent. carbon dioxid, his ventilation coefficient was only 163. This was exactly similar to what was observed on the previous occasion before he regained his compensation. However, at the second experiment the degree of dyspnea produced was not so great as at the first, although the percentage of carbon dioxid was just the same. Table 5 shows the essential features of this group.

TABLE 5.—CARDIAC DISEASE; COMPENSATED CASES

Subject	Rate of Respiration		Single Respiration, c.c.		Total Ventilation per Minute, Liters		Ventilation Coefficient at End	Per Cent. CO_2 in Inspired Air at End	Alveolar CO_2 Tension, mm.
	Initial	Final	Initial	Final	Initial	Final			
S. G. B.	19	28.5	675	850	12.74	24.30	191	3.92	39.3
	20.5	24	450	850	9.24	20.40	221	4.53	40.0
R. B.	20	30	525	775	10.71	23.02	216	4.85	39.2
J. H. B. ...	15	24	610	1,650	9.30	39.59	421	6.99	49.8
J. H. S	20	27	400	600	8.00	16.20	203	4.59	
	21	26	475	1,000	9.97	26.00	261	6.19	
A. F.	17.5	20.5	500	925	8.53	19.88	233	5.90	47.3
G.	18	19	400	822	7.20	15.62	217	5.40	36.2
T. H.	19	21.5	450	1,300	8.56	28.00	327	6.75	
	20	22.5	475	1,100	9.50	24.78	262	....	45.0
	19	22	525	1,150	9.98	25.30	253	5.97	
J. S.	22	24	450	700	9.90	16.80	170	4.48	
	22	30	450	800	10.35	28.00	270	5.62	43.5
	24.5	26	475	900	11.65	23.40	201	4.97	45.2
W. M.	14.5	20	450	600	6.52	23.40	360	4.60	38.1
	12	30	520	775	6.36	30.50	480	4.95	41.6
M. M.	18.5	28	700	950	12.95	21.80	163	5.32	

Pulse.—The greatest rise in pulse rate during these observations was 16 per minute. In most instances it was much less. In two cases a little exercise, insufficient to produce noticeable dyspnea, caused considerably greater rises in the pulse rate.

SUMMARY AND DISCUSSION

Experiments are described in which normal subjects and patients with cardiac or cardiorenal disease have breathed air containing

increasing amounts of carbon dioxid. The inspired air was analyzed for its carbon dioxid content, and the total ventilation of the subject per minute was measured at frequent intervals. Thus the increase in ventilation caused by a given rise of carbon dioxid in the inspired air could be easily determined. It was found that normal persons respond to carbon dioxid in a fairly constant manner, and that their total ventilation is doubled when the carbon dioxid is between 4.2 and 5.4 per cent. Cardiac and cardiorenal patients whose circulation is compensated, and who have no evidence of an acidosis as shown by the carbon dioxid tension of the alveolar air, behave in an exactly similar manner. Cases, however, with decompensation and with a grade of acidosis sufficient to lower the alveolar carbon dioxid tension react much more quickly to the carbon dioxid, and may double their ventilation when the carbon dioxid is only 2 to 3 per cent. of the inspired air. Dyspnea is therefore much more easily produced in the patients with acidosis than in those without acidosis. That the increased sensitiveness to carbon dioxid does in fact depend on the acidosis was especially clearly demonstrated in two cases. In one of these (J. W. O'M.) an observation made after the development of acidosis showed him to be more easily affected by carbon dioxid than he had been at a previous examination before the acidosis appeared. The second (J. P. C.) was extremely susceptible to carbon dioxid at a time when he had an acidosis, but after this had been overcome by large doses of sodium bicarbonate, in spite of the fact that his clinical condition had not improved, his reaction to carbon dioxid became exactly similar to that of normal individuals. Although the results reported relate only to the dyspnea caused by the inspiration of air containing carbon dioxid, it is wholly logical to assume that the same effect would be produced by acids which entered the blood stream from the body cells. The presence of an acidosis would thus render the organism more sensitive to the carbon dioxid or other acids formed during muscular work, and the amount of muscular work sufficient to cause dyspnea would be less than under normal conditions.

The explanation of these observations appears to be comparatively simple. Under normal circumstances the "buffer" action of the bicarbonates, phosphates and proteins in the blood is so great that a large amount of acid can be taken up without any significant change in the hydrogen ion concentration being produced. When, however, an acidosis is present which is severe enough to cause a depression of the carbon dioxid tension of the blood this mechanism for the preservation of the normal reaction of blood has begun to break down. The blood has already taken up nearly as much acid as it can without its reaction changing. When even a small additional amount of acid is

introduced into the blood there is an alteration of the hydrogen ion concentration, and a consequent stimulation of the respiratory center. Recent experiments by Christiansen, Douglas and Haldane[4] have a direct bearing on this subject. These authors found "that the presence of lactic acid in the blood" after severe exercise "led to an enormous temporary alteration in the absorption curve" for carbon dioxid, and they suggest that "corresponding differences in the normal absorption curve will probably be discovered under various pathologic or compensatory conditions of 'acidosis.'" The experiments reported here do not appear to give any information regarding possible changes in the excitability of the respiratory center in the pathologic conditions studied.

The importance of the observations lies in the fact that they throw some light on the part played by the acidosis in the production of dyspnea in cardiac, and especially in cardiorenal disease. The degree of acidosis, as indicated by the alveolar carbon dioxid tension, is, even when dyspnea is marked, rarely great in these conditions. A similar amount of acidosis in diabetes may cause no gross changes in the respiration. Moreover, the deep, regular breathing of diabetic coma, which is accepted as being the typical effect of acidosis, is wholly unlike the shallow, rapid, irregular respiration seen in cardiorenal dyspnea. It seems to be improbable that the acidosis is the sole cause of the dyspnea, but the experiments indicate that it is a contributing element, since it tends to break down the mechanism by which the normal reaction of the blood is maintained A subject with even moderate acidosis is rendered abnormally susceptible to any increase of the acid in his blood. Thus it is that certain patients with advanced chronic nephritis and low alveolar carbon dioxid tension have no dyspnea as long as the heart is sufficient, but as soon as the circulation begins to fail so that carbon dioxid and perhaps lactic acid accumulate in the blood the effect on the respiration is greater than it would be in a subject whose blood was normal. The extent to which the acidosis is involved in causing the dyspnea will depend on its severity and will vary from case to case.

The addition of carbon dioxid to the inspired air affects the respiration and produces little influence on the circulatory system. In normal persons the pulse rate only rises slightly even when the dyspnea is great. The same is true of compensated cardiac cases. A somewhat greater increase in pulse rate may be seen in the decompensated cases, but it is much less than the pulse rate which would be brought about if a similar degree of dyspnea were caused by exercise.

4. Christiansen, Douglas and Haldane: Jour. Physiol., 1914, xlviii, 244.

CONCLUSIONS

1. Normal individuals are affected in a fairly constant manner by breathing air containing increasing amounts of carbon dioxid. In the experiments reported the total ventilation was doubled when the concentration of carbon dioxid was between 4.2 and 5.4 per cent.

2. Patients with cardiac and cardiorenal disease, who are without acidosis, as indicated by the alveolar carbon dioxid tension, react in a manner similar to normal subjects.

3. Patients with cardiac and cardiorenal disease, with acidosis, are much more susceptible to the carbon dioxid in the inspired air. Dyspnea is more easily produced than in normal subjects or in patients without acidosis, and the ventilation may be doubled when the inspired air contains only 2 to 3 per cent. carbon dioxid.

4. While acidosis is probably not the sole factor causing the dyspnea in cardiac and cardiorenal disease, it may be an element of considerable importance in producing the clinical picture.

POISONING BY MERCURIC CHLORID AND ITS TREATMENT *

SAMUEL W. LAMBERT, M.D., AND HENRY S. PATTERSON, M.D.
NEW YORK

The recent increase in the number of cases of poisoning by mercuric chlorid is largely due to the newspaper notoriety which was given to a case of accidental poisoning occuring about four years ago. The public were instructed in all the details of the symptoms, and great stress was laid, not only on the sureness of the fatal ending, but also on the painlessness and lack of suffering which accompanied the week-long illness of that particular victim. The repetition of similar publications and the ease with which tablets of the drug could be obtained appealed to would-be suicides, and now both intentional and accidental cases of poisoning have become a common occurrence in hospital practice. Mercuric chlorid tablets have been used for some years as a household article to treat the ordinary slight wound infections of the family, to rid the house of bed vermin, and in many cases as a preventive of conception.

The commonest accident resulting in poisoning is the swallowing of the tablets in mistake for some headache remedy: such accidental cases about equal in number those of attempted suicide. In New York City the cases of suicide by poisoning, due to the principal drugs, for the past twenty-five years, are shown in Table 1, arranged in five-year periods.

This table shows that there is a fashion in the methods of suicides, and that poisoning by arsenic and Paris green and by phenol (carbolic acid) are on the decrease, that by opium is stationary, while poisoning by illuminating gas and mercuric chlorid are both becoming popular methods and are on the increase. Of the 155 cases of suicide by mercuric chlorid recorded in the past twenty-five years, seventy-three, or nearly half of them, have occurred in the last two years. This question, therefore, forms an important social problem. The regulation of the sale of the poison in the form of antiseptic tablets of corrosive sublimate is already begun, and should be undertaken and enforced by all boards of health.

The symptoms of poisoning by mercuric chlorid came into prominence and were studied first as a complication of surgical operations and in obstetric practice. The drug was introduced as an antiseptic

* Submitted for publication June 8, 1915.

in the early eighties, and has been widely used ever since. In the cases of wound absorption, the initial toxic gastritis is absent, and the kidney symptoms and salivation are less prominent than the colitis. The absorption of the drug is gradual in these cases, and its effect is shown in great part in the efforts of the large intestine to eliminate it, with the result of an intensive and often fatal ulcerative colitis. A case of mercuric chlorid poisoning, resulting from the surgical accident of delivering about 1½ grains of the salt into the vein of a patient during a postoperative saline infusion, gave the following sequence of events, and throws much light on the symptomatology of the condition. The symptoms in this case are not the same as those which result from absorption from surgical wounds, but resemble the cases of poisoning with a predominance of kidney and intestinal symptoms.

TABLE 1.—SUICIDES IN NEW YORK BY POISONING, 1890-1914

Poisons	1890-1894	1895-1899	1900-1904	1905-1909	1910-1914
Paris green and arsenic	155	170	99	47	48
Phenol	73	627	1,455	225	154
Opium and morphin	42	56	56	48	29
Mercuric chlorid	4	10	9	28	104
Illuminating gas	65	315	628	1,149	1,554
Other poisons	58	94	104	196	237
Total all poisons	397	1,272	2,351	1,793	2,126

Figures from 1890 to 1897 inclusive represent former City of New York.
Figures from 1898 to 1914 inclusive represent Greater New York.

The infusion was given on the fifth day after a laparotomy. Prior to the giving of the drug, the patient had passed about 30 ounces of urine a day, and had had a daily evacuation of the bowels as the result of enema or saline catharsis. There was no previous vomiting, and the pulse ranged from 80 to 90. The wound was slightly infected, and the temperature ranged from 100 to 101.8. The infusion was given because of postoperative sepsis of mild type. Eight hours after the infusion, the patient vomited, and the pulse became irregular and weak. The vomiting was repeated several times during the first twenty-four hours. The secretion of urine was interfered with from the start, and about 2 ounces were secreted during this period. During the second twenty-four hours, 2½ drams of urine were obtained by catheter, and the bowels began to move involuntarily and continuously. The pulse was irregular and weak, the rate about 120 and the breathing was labored. The involuntary stools continued, and became bloody and full of mucus. Nine drams of urine were drawn by catheter during the day.

The following thirty-six hours presented the same symptoms of a severe colitis, and an almost total suppression of urine, and the patient died in extreme exhaustion five and one-half days after the infusion, without improvement in the colitis or the urinary symptoms. There was marked mental distress, but none of the ordinary symptoms of uremia.

A necropsy was held in this case, and its true etiology was first discovered by the microscopic appearance of the kidneys. The essential findings of the postmortem examination were as follows:

The heart was normal. The lungs showed some congestion and edema of lower lobes. There were large masses of clotted blood in the gastrohepatic ligament, the gastrocolic and the gastrosplenic ligament, and in the lesser peritoneal cavity. The gallbladder had been removed at the laparotomy. The liver was very friable and deeply bile stained. The bile ducts were much thickened and dilated, and contained many small black calculi. In the common duct there was a stone about 6 mm. in diameter. The spleen showed nothing special. The kidneys were very large and deeply jaundiced; there were several cysts on the surface. The capsule stripped with some difficulty, leaving the surface roughish. On section, the kidneys were very edematous and showed evidence of acute degeneration; the color was pale yellow with small hemorrhagic spots. The mucous membrane of the stomach was very much swollen, very red and covered with a layer of thick mucus. The intestines were filled with blackish watery feces, mixed with a large amount of mucus. The descending portion of the colon and sigmoid were covered with membrane and deeply congested. The lesion was most severe in the sigmoid. The glands were normal.

The anatomic diagnosis was fixed as: hemorrhage into the lesser peritoneal sac and gastric ligaments, chronic diffuse nephritis with acute degeneration, general jaundice, biliary calculi in bile ducts.

The microscopic examination of the organs showed biliary pigmentation in the liver cells and bile capillaries, and also in the kidney cells. The kidneys showed an extensive parenchymatous degeneration and calcification of the walls of the convoluted tubules, with large casts which are still present in the tubules. There is a small amount of connective tissue between the tubules. The glomeruli show no important lesions. These changes in the kidney are those characteristic of poisoning by mercuric chlorid.

In the cases of poisoning caused by swallowing the drug, the symptoms begin promptly after it is taken. Abdominal distress and pain at first in the epigastrium and later more general, are the primary symptoms. Nausea and vomiting of the stomach contents and later of mucus, which is more or less blood stained, accompanies the pains. This gastritis is usually promptly treated with egg albumin or milk and lavage, and yields quite readily to such treatment, so that the patient is comparatively comfortable after thirty-six hours' rest and abstinence from food. The mouth shows signs of a mercurial stomatitis in about twenty-four hours, but this rarely is so severe as usually accompanies salivation from calomel. If the poisoning is left to run its course uninfluenced, the patient's attention is called to the diminishing amounts of urine in from forty-eight to seventy-two hours after taking the drug. This may develop to a complete anuria, and the patient dies without restoration of the secreting power of the kidneys. When this occurs, the patient may remain free from cerebral symptoms for the better part of a week, until a terminal form of low delirium supervenes and a weakening heart action proves fatal. There are none of the regular evidences of uremia, and convulsive seizures do not occur. If the kidney condition is survived and its function

reestablished, and in those cases which do not develop this extreme degree of nephritis, there is apt to be a membranous colitis with deep ulcerations and hemorrhages, which may develop and prove fatal even after several weeks have elapsed from the time of the original poisoning.

In a case recently observed by one of us in consultation outside the hospital, a patient, who denied having taken the drug, had been anuric for three days. Calculus anuria was suspected, but an examination by Roentgen ray showed no stone, and examination of a stool revealed the presence of mercury. Free colonic irrigations were begun, and after five days of anuria, the patient passed 1 dram, on the following day 5 drams, and then the daily amount slowly rose until, after about a week or ten days of reestablished urination, he was passing over 50 ounces of urine. Notwithstanding this, at about the end of three weeks, he developed a severe colitis, with the passage of large casts of the colon, and died, after a large intestinal hemorrhage.

The therapeutics of mercuric chlorid poisoning up to the present have been quite unsatisfactory. The patients have regularly developed anuria on or about the fourth day after taking the poison, and progress to subsequent death, from lesions of the liver and colon, with or without the reestablishment of the urinary secretion.

Radical procedures have been tried in such cases, including the surgical manipulations of loosening the kidney capsule; but it may well be doubted if such operative treatment has had any specific influence on the course of the clinical picture. The following treatment has been gradually formulated as the result of caring for ten consecutive cases of varying severity which have all resulted in a cure. The first two cases of poisoning resulted from the insertion of two tablets (15 grains) into the vagina, and was treated by favoring the elimination of the poison by frequent and prolonged colonic irrigations with normal saline and by such local measures as were needed to allay the severe vaginitis.

The remaining cases were due to swallowing one or more of the commonly used tablets containing 7½ grains of mercuric chlorid. The treatment in the detail now used at St. Luke's Hospital as a routine has been elaborated through the help of the method of Vogel,[1] by which mercury is readily detected in stomach contents, urine and stools. By this procedure one can determine not only the diagnosis and the necessity of beginning treatment, but also, in some cases, the length of time treatment should be continued. A certain number of

1. Vogel, K. M., and Lee, O. I.: Detection of Mercury in the Excretions. Jour. Am. Med. Assn., 1914, lxii, 532.

patients are brought to institutions either pretending to have taken mercuric chlorid, or fearing that they have taken it by mistake in the dark, etc. It is particularly important to know if a patient has not taken the poison, for the treatment is most irksome to the patient, and entails unusual activity on the part of the nursing department.

Vogel's method consists of separating the mercury from its albuminous combinations in the organic material to be examined and then subliming it in a sealed tube to form an amalgam on a small piece of dentist's gold. Dr. Vogel states that:

> If mercury is present it will manifest itself by the appearance of a silvery patch of amalgam on the gold foil. If the amount of the metal is exceedingly minute there will be simply a pale discoloration of the gold, seen to better advantage with the hand-lens or by removing the pellet from the tube and examining it with the low power of the microscope, but if the amount is larger the deposit on the gold will be very easy to recognize.

Before outlining the treatment, attention is directed to some characteristics of these cases which have been treated by us and studied by Vogel's method of detecting mercury in excreta.

In the first place, it has been found that mercury, in cases of mercuric chlorid poisoning, is regularly found in the stomach for several days after the ingestion of the poison. That it is not wholly swallowed in the saliva but is secreted by the stomach in an effort to eliminate it from the body, and that it is not part of the poison held in combination with the mucous membrane of the stomach, seem to be indicated by the fact that after several days the tests are negative, to become positive again before all the mercury is eliminated. This corresponds to the behavior of the tests conducted on urine and feces, late in the poisoning. Certain experiments are given below which indicate the same thing.

Another feature which is a determining factor in the length of time treatment should be carried on is the behavior of the mercury elimination after the patients, apparently, are entirely recovered. A reference to the summaries of the tests for mercury under the case histories will show the very long time it takes to free the system of mercury after mercuric chlorid poisoning. In Case 6, in which nephritis existed before the poisoning, in Case 7, in which successive doses were taken, and in Case 8, in which a large dose was taken, the excretion of mercury by the kidneys, the colon and the stomach lasted for days after all symptoms had cleared up. It has become quite apparent that treatment need not be kept up after the urine, and particularly the stools, begin to show negative results.

The treatment, as it is formulated at present for cases coming under observation early, is as follows: The first indication is to give the patient the whites of several eggs and then to wash out the stomach thoroughly. This has usually been done before the patients are admitted to the hospital. On admission, the stomach contents are expressed and examined for mercury, the stomach is thoroughly washed, and a pint of milk introduced. If no stomach contents are obtained before lavage, then the lavage water is examined for mercury. Urine passed spontaneously, or that obtained by catheter, is examined for mercury. The metal appears in the urine in from three to twenty-four hours after it has been swallowed. If more than a day has elapsed since the poisoning occurred, a stool should also be examined for the poison. If the first lavage does not allay the nausea and vomiting, it is repeated after an hour, and the following routine is begun as soon as the stomach will permit:

1. The patient is given every other hour 8 ounces of the following mixture: Potassium bitartrate, 1 dram; sugar, 1 dram; lactose, one-half ounce; lemon juice, 1 ounce; boiled water, 16 ounces. Eight ounces of milk are administered every alternate hour.

2. The drop method of rectal irrigation with a solution of potassium acetate, a dram to the pint, is given continuously. The amounts of urine secreted under this treatment are very large. In Case 8, 269 ounces were passed in twenty-four hours on the fourteenth day of treatment.

3. The stomach is washed out twice daily.

4. The colon is irrigated twice daily, in order to wash out whatever poison has been eliminated in that way.

5. The patient is given a daily sweat in a hot pack.

It is imperative to emphasize the necessity of keeping up the treatment with the colonic drip enteroclysis day and night without interruption. It entails discomfort for the patient, but the victims of accidental poisoning are always willing to do anything to recover from their plight, and the attempted suicide usually repents rapidly of his error, and the hope of his life being saved stimulates his patience and desire to cooperate.

In cases in which one single dose has been taken, after two negative examinations of the urine, on successive days, it seems legitimate to stop the treatment. In the fifth case, the urine was found to contain no mercury on at least two examinations before discharge. In view of the behavior of subsequent cases, which have been more thoroughly studied, it is probable that this patient excreted mercury for some time after leaving the hospital. For the less severe cases, a week

may be a sufficient time for treatment. When large or successive doses have been taken, or when there is a preexisting kidney lesion, or when treatment begins several days after the poison is taken, longer periods of treatment, up to three weeks, are necessary.

It is interesting to consider how much damage the kidney suffers as a result of eliminating, even in a highly diluted form, an amount of mercury which hitherto in medical experience has led to fatal results. That such damage is not always great is indicated by the fact that in Case 5, 76 per cent. of phenolsulphonephthalein was excreted in two hours, the second day that the man's urine was free from mercury. In Case 3, the phenolsulphonephthalein excretion was 55 per cent. Six weeks after discharge the patient was apparently free from sequelae of her poisoning.

With one exception all these cases came under treatment within twenty-four hours of taking the poison. In cases which have reached the stage of anuria, however, favorable results cannot always be expected. While it is perfectly possible to reestablish urination, the cases quite regularly go on to a fatal termination, with degenerative liver changes, and a colitis of the so-called diphtheritic type. In one of the present cases, Case 6, in which there was preexisting nephritis, the urinary output was reduced to 32 minims in twenty-four hours on the fifth day after taking the drug in spite of the fact that treatment was begun three hours after the poisoning. Recovery resulted, but the treatment was much longer than usual. Two of the patients were in the hospital over six weeks and gave positive Wassermann reactions, which were entirely unaffected by the poisoning.

Under the treatment detailed above, these patients quiet down to their routine and, as a rule, do not suffer except from the discomforts of the therapeutic measures. The stomach becomes tolerant of the milk diet and the alkaline drink after from twenty-four to thirty-six hours. The kidney secretion at first is excessive, and may run up to 130 or more ounces in the twenty-four hours. This usually diminishes in spite of the continued exhibition of fluid between the fifth to the tenth day, and may nearly stop altogether, as in Case 6. It is at this period that the continuous water cure and the rest in bed must be insisted on. If this period is successfully passed, the secretion of urine again increases often to a higher level than at first. The mercury itself seems to act as a diuretic at this stage of the treatment. The bowels usually show some irritation, but when the treatment is faithfully carried out, the tendency to diarrhea and colitis is regularly controlled by the colonic irrigations, and other medication for this symptom has been rarely necessary.

In order to clear up some of the toxicologic points which have been raised by the study of these cases, Professor Lieb has carried out the following experiments in the pharmacology laboratory at the College of Physicians and Surgeons: Several animals were operated on under narcosis, and after the esophagus had been tied off so that no connection was left between the pharynx and the stomach, a hypodermic dose of mercuric chlorid was given. The excretion of the poison was then studied by the Vogel method. Three series of experiments were done. In Series 1, two rabbits were used. After the preliminary operation each received 20 mg. of mercuric chlorid hypodermically. After a few hours, mercury was found in the contents of the stomach and in that of the colon of both animals. In Series 2, three decerebrated cats were employed and prepared in the same way as given above. The presence of mercury was demonstrated in two of these animals in the urine and feces, and also in the stomachs after from four to eight hours. In Series 3, five decerebrated cats were again experimented on, and both the esophagus and the duodenum were tied off. From 15 to 20 mg. were injected into the jugular vein. Three cats gave a positive reaction after from six to eight hours. Another line of investigation concerning the elimination of mercury was made in the wards. Two patients who needed hot packs were receiving weekly hypodermic doses of mercuric salicylate. In both cases pads of filter paper were placed on the skin of the axilla, and after being saturated in the sweat of the patients, reacted positively to the Vogel test for mercury.

Case 1.—Admitted December 8. Three days before admission, patient had inserted two 7½-grain mercuric chlorid tablets in the vagina to relieve pain in the lower abdomen. Soon afterward she began to have severe abdominal pain, and her mouth became sore and salivated. She had vomited four times before admission.

The patient appeared ill and uncomfortable; the mouth was foul, with sordes on teeth and gums; tongue was badly coated; there was moderate salivation; tonsils and pharynx were congested, and the parotid gland on each side was swollen and tender. In the vagina there were yellow and dark brown sloughs on the inner side of each labium major, also yellow and white sloughs on both sides of vagina. The cervix was red and swollen, and there was a watery discharge from the os uteri.

December 9, saline douche was ordered twice daily, and gastric lavage was given, followed by castor oil, through the tube. Colon irrigation (4 gallons) was repeated twice daily.

December 23, patient's condition had decidedly improved in last few days; mouth was much cleaner; she still had a vaginal discharge. Patient left hospital against advice, and was reported well three years later.

EXTRACT FROM URINE CHART, CASE 1

Date	Amount, c.c.	Reaction	Sp. Gr.	Albumin	Sugar	Microscopic
Dec. 9	720	Acid	.....	Trace	0	Many red blood cells
Dec. 10	840	Acid	.....	0	0	No blood (catheterized)
Dec. 11	900	Acid	1.030	Trace	0	Urates, no casts found
Dec. 12	540	Acid	.....	Trace	0	Pus cloud
Dec 13	750	Acid	1.036	Trace	0	Pus sediment
Dec. 14	840	.....	.....	.....	...	
Dec. 15	540	Acid	1.030	Trace	0	Pus cloud
Dec. 16	420	Acid	1.030	Trace	0	Pus and blood sediment
Dec. 17	660	Acid	.....	.....	0	Pus and blood sediment
Dec. 18	540	Acid	1.014	Trace	0	Pus cloud
Dec. 19	420	Alkaline	1.035	Trace	0	Pus cloud
Dec 20	420	Acid	.....	Trace	0	Few leukocytes and ep. cells
Dec. 21	960	Alkaline	1.026	Faint trace	0	Hyaline casts

CASE 2.—Admitted November 21. On the morning of the day of admission at 2 a. m., patient had inserted one 7½-grain mercuric chlorid tablet in vagina to avoid conception. Soon afterward she had severe burning sensation in that region and attempted douching, without success. Realizing the gravity of the situation, she came to the hospital, complaining less of pain in the vagina, than peculiar paresthesia and cramplike pains in hands and feet. No salivation was evident.

Physical examination was negative, except for a good deal of redness of vulva, with seropurulent discharge from vagina. Mucous membrane of vagina was covered with a white slough. Cervix was red.

Treatment was ordered as follows: an alkaline douche twice daily, forced fluid diet, a saline colon irrigation twice daily. The patient was discharged from the hospital at the end of a week.

EXTRACT FROM URINE CHART, CASE 2

Date	Amount, c.c.	Reaction	Sp. Gr.	Albumin	Sugar	Microscopic
Nov. 21	1,020	Acid	1.008	Faint trace	0	Many leukocytes; no casts
Nov. 22	2,220	Alkaline	1.006	Faint trace	0	Few hyaline casts
Nov. 23	4,220	Alkaline	1.008	Faint trace	0	Few hyaline casts
Nov. 24	3,990	Alkaline	1.008	Faint trace	0	Few hyaline casts
Nov. 25	4,920	Alkaline	1.014	Faint trace	0	

CASE 3.—Admitted February 12. Twenty-four hours previously she had swallowed three 7½-grain mercuric chlorid tablets in mistake for soda mints. Immediately she drank milk mixed with eggs, and a doctor arriving half an hour later washed out her stomach. She began to vomit soon after taking tablets, but this was relieved by the lavage. Six hours ago she began to have epigastric pain and abdominal cramps, accompanied by diarrhea. Urine was scanty and she had headache and sore throat.

EXTRACT FROM URINE CHART, CASE 3

Date	Amount, c.c.	Reaction	Sp. Gr.	Albumin	Sugar	Microscopic
Feb. 12	180	Acid	1.025	Marked trace	0	Few hyaline casts
Feb. 13	750	Neutral	1.022	Marked trace	0	Hyaline and gran. casts
Feb. 14	2,450	Alkaline	1.019	Marked trace	0	Hyaline and gran. casts
Feb. 15	1,500	Alkaline	1.013	Marked trace	0	Pus cloud
Feb. 16	400	Acid	1.029	Marked trace	...	Hyaline and gran. casts
Feb. 17	925	Neutral	1.021	Faint trace	+	Hyaline casts
Feb. 18	600	Alkaline	1.013	Faint trace	...	Hyaline casts
Feb. 19	900	Neutral	1.013	Faint trace	...	Leukocytes
Feb. 20	900	Neutral	1.016	Faint trace	0	Leukocytes
Feb. 21	950	Alkaline	1.017	Faint trace	0	Leukocytes
Feb. 22	1,800	Acid	1.011	Faint trace	0	Leukocytes
Feb. 23	1,500	Acid	1.012	Faint trace	0	Pus cloud
Feb. 24	2,400	Acid	1.014	Faint trace	0	Pus cloud
Feb. 25	800	Alkaline	1.015	Faint trace	0	Pus cloud
Feb. 26	400	Acid	1.012	Faint trace	0	Leukocytes
Feb. 27	550	Acid	1.015	Faint trace	0	Leukocytes
Feb. 28	425	Alkaline	1.016	Faint trace	0	Leukocytes

Phenolsulphonephthalein excretion, February 12, 51 per cent.
Phenolsulphonephthalein excretion, February 28, 55 per cent.

Physical examination was negative, except for general abdominal tenderness, most intense over lower half.

On admission the patient was put on a continuous rectal irrigation by the drop method, containing potassium acetate 1 dram to the pint. This was continued from February 12 to 17; patient then complained of soreness about rectum, and of the proctoclysis making her very nervous. She was then given a colon irrigation each day for four days, when the proctocylsis was again started, and continued until discharge. Hot packs were given daily while the patient was in the hospital. The lumbar region over the kidneys was cupped every three hours during the first three days she was in the hospital.

Patient left the hospital, February 28, in very good general condition, and although advised to remain in hospital until urine was clear of albumin, she left against advice.

CASE 4.—Admitted November 11. On night of admission, patient took two 7½-grain mercuric chlorid tablets. She arrived in the hospital in less than an hour, where stomach was washed. Past history was negative, except that one year before this she was treated for two months for "kidney trouble."

Physical examination revealed the right kidney distinctly palpable, but otherwise was negative.

November 11, mercury present in both vomitus and urine.

November 12, treatment was started on continuous rectal irrigation by the drop method, containing potassium acetate one-half ounce to quart of water.

November 18, patient left the hospital cured, although no examination for mercury was noted at time of discharge.

CASE 5.—Admitted January 23. About one hour before admission patient took two tablets which he thought were headache medicine. Ten minutes later he had burning pain in stomach and took a glass of milk which gave slight

EXTRACT FROM URINE CHART, CASE 4

Date	Amount, c.c.	Reaction	Sp. Gr.	Albumin	Sugar	Microscopic
Nov. 11	.....	Acid	1.015	Trace	0	Many hyaline casts
Nov. 12	1,770	.....	.....	.....	...	No blood, no casts
Nov. 13	2,440	Acid	1.005	0	0	Few leukocytes
Nov. 14	4,070	Acid	1.005	0	0	Few leukocytes
Nov. 15	4,220	Acid	1.010	0	0	Few leukocytes
Nov. 16	3,630	Alkaline	1.010	Trace	0	Few leukocytes
Nov. 17	1,340	Alkaline	1.010	0	0	Few leukocytes
Nov. 18	.....	Acid	1.005	0	0	Few leukocytes

relief. The pain continued, and he came to hospital. He vomited in examining room and was given a gastric lavage (both of which proved to contain mercury). Patient brought a tablet of the medicine with him, which proved to be the ordinary 7½-grain tablet of mercuric chlorid. On being sent to ward, he was given another gastric lavage lasting fifteen minutes, then drank one pint of milk, one-half hour later the stomach was again washed clean (this is the lavage reported January 24 as containing mercury). He was put on milk diet, continuous proctoclysis (drop method) with potassium acetate, 1 dram to pint of water. Potassium bitartrate solution, 8 ounces, was ordered every hour. Patient was discharged, January 31.

EXTRACT FROM URINE CHART, CASE 5

Date	Amount, c.c.	Reaction	Sp. Gr.	Albumin	Sugar	Microscopic
Jan. 23	2,550	.....	1.008	Very faint trace	0	Few leukocytes and ap. cells
Jan. 25	2,200	Neutral	1.010	Faint trace	0	Few leukocytes and ap. cells
Jan. 26	3,100	Neutral	1.008	Faint trace	0	Many leukocytes and triple phos. crystals
Jan. 27	3,900	Alkaline	1.010	Faint trace	0	Few leukocytes and ap. cells
Jan. 28	1,025	Neutral	1.010	Very faint trace	0	Few leukocytes
Jan. 29	1,950	Alkaline	1.010	Faint trace	0	Few leukocytes and ap. cells
Jan. 30	2,350	Neutral	1.010	Faint trace	0	Few leukocytes and ap. cells
Jan. 31	600	Acid	1.020	Very faint trace	0	Few leukocytes and ap. cells

January 29, phenolsulphonephthalein test, first hour, 50 per cent.; second hour, 26.5 per cent.; total, 76.5 per cent.

SUMMARY OF TESTS FOR MERCURY, CASE 5

	Jan. 23	Jan. 24	Jan. 25	Jan. 26	Jan. 27	Jan. 28	Jan. 29
Urine.....	Positive	Positive	Positive	Positive	Positive	Negative	Negative
Vomitus.....	Positive	.....	.....	.....	.....	.....	.....
Lavage.....	Positive	Positive	.....	.....	.....	.....	.....
Stool.....	.....	Positive	Positive	.....	.....	.....	.....

CASE 6.—Admitted March 26, at 5:45 p. m. At 3 p. m., patient took four 7½-grain mercuric chlorid tablets. Shortly after this she took some castor oil and mustard water which made her vomit. At 4 o'clock she was seen by a physician who gave her a thorough gastric lavage and some milk.

The past history of the patient revealed that she had had an interstitial keratitis and was given two doses of salvarsan and a prolonged mercurial treatment. One other sister had congenital syphilis. The Wassermann reaction is said to be positive in both her sister and herself.

Physical examination was unimportant. The routine treatment as outlined in this article was carried out beginning March 26 and continued for more than five weeks. March 26, the vomitus and lavage water were both positive for mercury. The stools, the urine and the gastric lavage were positive to the mercury tests for a period of several weeks. March 28, the first negative test occurred in the gastric lavage. May 2, the first negative test was found in the urine. May 16, the stool was negative for the first time. The mercury was not completely eliminated by July 3 and occasional positive results were found up to that date, when the examinations were stopped.

EXTRACT FROM URINE CHART, CASE 6

Date	Amount, c.c.	Reaction	Sp. Gr.	Albumin	Sugar	Microscopic
Mar. 27	395	Acid	1.010	Faint trace	0	Hyaline and gran. casts
Mar. 28	127	.....	.....	.....	...	
Mar. 29	45	.....	.....	.....	...	
Mar. 30	45	.....	.....	.....	...	
Mar. 31	7	.....	.....	.....	...	
Apr. 1	55	.....	.....	.....	...	
Apr. 2	395	.....	.....	.....	...	
Apr. 3	955	.....	.....	.....	...	
Apr. 6	1,405	Neutral	1.010	Faint trace	0	Few leukocytes, hyaline casts
Apr. 11	660	Alkaline	1.015	Marked trace	0	Few leukocytes
Apr. 13	1,310	Neutral	1.010	Trace	0	Pus cells
Apr. 30	3,991	Alkaline	1.002	Very faint trace	0	Few leukocytes
May 10	4,640	Neutral	1.005	Very faint trace	...	Few leukocytes

The striking feature in this case is that on March 31 there was an almost complete suppression, and when the twenty-four-hour secretion was only 32 minims. March 26, the Wassermann reaction was double plus, and on April 24 it was four plus.

The phenolsulphonephthalein excretion in two hours was as follows: April 7, 3.3 per cent.; April 9, 4 per cent.; April 17, 41 per cent.; April 23, 47.5 per cent.; May 10, 71.4 per cent.

CASE 7.—Admitted April 9. Four days ago patient took one 7½-grain mercuric chlorid tablet. The only symptom complained of is that she vomited a little later. Twenty-four hours ago, she took two more 7½-grain tablets, and about an hour later had pain in the abdomen for which she took some "soda." After this she vomited several times. About 3 o'clock this afternoon, she swallowed another 7½-grain mercuric chlorid tablet, and vomited about half an hour later. The bowels have moved several times a day for the last few days, but she has felt fairly well since taking the first tablet except for a

burning sensation in abdomen, and headache, and has had no appetite. She has noticed no decrease in amount, or change in character of urine.

Physical examination was unimportant. The routine treatment was given and continued for two months, although the symptoms of poisoning were practically absent after the first days of gastric irritation. The tests for mercury were positive for many days both in the urine and the stools and the gastric lavage. The first negative examination in the urine was on April 27, and in the feces on June 8. But the mercury was not completely eliminated by July 3. Occasional positive results were obtained up to that date, when the examinations were stopped.

EXTRACT FROM URINE CHART, CASE 7

Date	Amount, c.c.	Reaction	Sp. Gr.	Albumin	Sugar	Microscopic
Apr. 10	1,175	Acid	1.010	Faint trace	0	Many leukocytes
Apr. 12	600	Alkaline	1.010	Very faint trace	0	Many leukocytes
Apr. 13	1,600	Neutral	1.015	Faint trace	0	Many leukocytes; mucus
Apr. 17	3,500	Alkaline	1.005	Trace	0	Many leukocytes
Apr. 30	.....	Alkaline	1.010	Very faint trace	0	Few leukocytes
May 10	.....	Neutral	1.015	Very faint trace	0	Many leukocytes
May 20	1,500	Neutral	1.010	Faint trace	0	Many leukocytes
May 22	.....	Neutral	1.010	Trace	0	Many leukocytes
June 7	.....	Acid	1.005	Very faint trace	0	Many leukocytes
June 22	.....	Neutral	1.005	Faint trace	0	Many leukocytes
June 23	1,800	Neutral	1.015	Trace	0	Few leukocytes
June 28	.....	Alkaline	1.005	Trace	0	Few leukocytes
July 1	.....	Acid	1.015	Trace	0	Few leukocytes

The phenolsulphonephthalein excreted in two hours was as follows: April 9, 66.5 per cent.; April 21, 62.5 per cent.; June 22, 65 per cent.

CASE 8.—Admitted June 14. About an hour and a half before admission to the hospital, patient took by mistake six 7½-grain mercuric chlorid tablets, dissolved in water, in mistake for a sleeping mixture. She drank a glass and a half of water after this. In a few minutes she felt great discomfort in her throat, and vomited a large amount. She was given three raw eggs, a doctor was called and she was sent to the hospital. Her physical examination was negative. The symptoms need not be given here. The routine treatment was instituted.

June 14, the urine was positive to the mercury test, but the gastric lavage on admission was twice negative. It became positive on the 15th, and remained so until the 17th, after which it was negative. June 23, the urine was negative for the first time, and on July 20 the first negative stool was examined. The elimination of mercury was not complete at time of discharge, July 28.

CASE 9.—Admitted July 11. About three hours before admission, patient took one 7½-grain tablet of mercuric chlorid by mistake for aspirin. He went to a doctor's office immediately and in about fifteen minutes was given mustard and vomited several times. The stomach was then washed out thoroughly and patient drank milk. After that he was sent to the hospital. Distress in abdomen followed the lavage, but there was no actual pain. The bowels were regular, the urination was normal, the appetite good.

Physical examination was negative and the routine treatment was begun. July 11, the urine, stool, vomitus and lavage were all positive to mercury. July 24, the first negative urine was found, but there were no negative stools before leaving the hospital.

EXTRACT FROM URINE CHART, CASE 8

Date	Amount, c.c.	Reaction	Sp. Gr.	Albumin	Sugar	Microscopic
June 14	1,008	Alkaline	1.025	Very faint trace	0	Mucus
June 16	2,650	Alkaline	1.005	Very faint trace	0	Many leukocytes
June 22	5,007	Neutral	1.005	Faint trace	0	Few leukocytes
June 24	4,092	Alkaline	1.005	Very faint trace	0	Few leukocytes
June 28	2,196	Alkaline	1.010	0	0	Few leukocytes
July 1	.....	Alkaline	1.016	Trace	0	Few leukocytes, hyaline and gran. casts
July 4	5,911	Alkaline	1.005	0	0	Few leukocytes
July 6	6,764	Alkaline	1.005	Faint trace	0	Few leukocytes
July 9	.....	Alkaline	1.020	Very faint trace	0	Few leukocytes
July 11	5,484	Alkaline	1.005	0	0	Few leukocytes
July 14	.....	Alkaline	1.005	0	0	Few leukocytes
July 17	4,916	Alkaline	1.010	0	0	Few leukocytes
July 19	4,052	Alkaline	1.005	0	0	Few leukocytes
July 23	.....	Alkaline	1.005	Faint trace	0	Few leukocytes

June 14, the phenolsulphonephthalein excretion in two hours was 55.5 per cent, and on July 14, it was 45.7 per cent. July 14, the Wassermann reaction was two plus in spite of the excessive dose of the mercury.

EXTRACT FROM URINE CHART, CASE 9

Date	Amount, c.c.	Reaction	Sp. Gr.	Albumin	Sugar	Microscopic
July 11	1,950	Acid	1.010	Very faint trace	0	Few ep. cells, hyaline casts
July 12	3,930	Neutral	1.005	Faint trace	0	Few ep. cells, hyaline casts gran. casts
July 13	3,656	Neutral	1.005	0	0	Epithelium
July 14	4,204	Acid	1.010	Very faint trace	0	Epithelium
July 15	2,833	Acid	1.015	Very faint trace	0	Epithelium
July 16	3,900	Acid	1.010	Very faint trace	0	Epithelium
July 17	3,920	Acid	1.013	Faint trace	0	Epithelium
July 18	4,288	Acid	1.010	Faint trace	0	Epithelium, occasional gran. cast
July 19	2,980	Neutral	1.005	Very faint trace	0	Epithelium and mucus
July 20	4,022	Neutral	1.005	Very faint trace	0	Epithelium and mucus
July 21	2,376	Neutral	1.005	Very faint trace	0	Epithelium and mucus and leukocytes
July 22	3,686	Neutral	1.005	Very faint trace	0	Epithelium and mucus and leukocytes
July 24	.....	Alkaline	1.020	Faint trace	...	Epithelium and mucus and leukocytes

July 24, phenolsulphonephthalein test showed 55.8 per cent. excretion in two hours.

EXTRACT FROM URINE CHART, CASE 10

Date	Amount, c.c.	Reaction	Sp. Gr.	Albumin	Sugar	Microscopic
Mar. 22	2,737	Acid	1.025	Faint trace	0	Pus cloud
Mar. 24	8,107	Alkaline	1.010	Faint trace	0	Many leukocytes
Mar. 26	3,107	Alkaline	1.010	Very faint trace	0	Occasional gran. cast
Mar. 30	5,778	Acid	1.010	Very faint trace	0	No casts

CASE 10.—Admitted March 21. Patient took by mistake three tablets of mercuric chlorid dissolved in 6 ounces of water, as a gargle, and swallowed practically all of it. She vomited fifteen minutes later a greenish fluid. Pain in the epigastrium followed immediately, and patient came at once to the hospital where she vomited again, a thick, foamy, colorless mucus. The patient came under treatment within an hour after poisoning. There were no symptoms after the first two days, and the treatment was routine. She was discharged March 31. All the excreta and stomach washings were positive to mercury for three days. The stomach washing was first negative on March 24, to be again positive March 27. The urine was first negative on March 24 and positive at intervals until treatment ceased, March 31. The colon irrigations were positive until March 30.

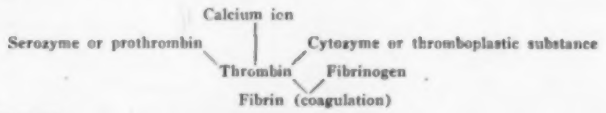
130 East Thirty-Fifth Street—130 East Sixty-Second Street.

THE COAGULATION TEST FOR SYPHILIS, AS DEVISED BY HIRSCHFELD AND KLINGER *

HAROLD NEWTON COLE, M.D.
AND
SAMUEL ENG-KIU CHIU, M.D.
CLEVELAND

Since the first appearance of the Wassermann test for syphilis, many short cuts and modifications have been devised or suggested and, we regret to say, most of them have failed to stand the test of time as well as the original. Moreover, several entirely new methods of diagnosis have been devised, of which Noguchi's cutaneous test has probably come the closest to being satisfactory, and that only in certain stages of the disease. In 1914, Hirschfeld and Klinger reported to the Congress of Internal Medicine at Wiesbaden that they had succeeded, by means of the process of coagulation, in distinguishing a syphilitic from a nonsyphilitic serum. At that time they had examined about 250 serums; they later reported that about 500 had been tested by a collaborator, and since then, in a personal communication, have written that around 1,000 successful tests have been made. During the past nine months, we have also been working with the technic, and have now done about 600 tests which we wish to report.

The reaction is based on the phenomena of coagulation of the blood. Hirschfeld and Klinger conceived the idea that there might be possibly a deviation of the cytozyme, akin to the deviation of the complement in the Wassermann reaction. To understand the details, it will be necessary to recall several of the principles of coagulation of the blood; and as Hirschfeld and Klinger have worked entirely on the schema as given by Bordet and Delange, we will only mention the work of these authors—it being outside the scope of this paper to discuss coagulation of the blood in its entirety. According to this schema, as we can see, coagulation is due to the precipitation of the fibrinogen of the plasma by the thrombin.



* Submitted for publication June 29, 1915.

* From the Department of Dermatology and Syphilis, the H. K. Cushing Laboratory of Experimental Medicine, and the Department of Pathology of Western Reserve University and Lakeside Hospital.

The thrombin itself is the product of three factors: first serozyme; an albuminoid thermostabile substance contained in the plasma; second cytozyme, a thermostabile substance, lipoid in nature, derived from tissues of the body, blood cells, platelets, etc., and very similar to lecithin and cephalin; third, calcium in the state of ionization (the non-ionized salts, for example, citrate, Arthus, Sabbatini and others have shown to be not active). The thrombin forms itself only in the presence of calcium, only a few seconds of time being required, and, once formed, it provokes coagulation of the fibrinogen, even in the absence of the ionized calcium salts. Bordet and Delange have shown that 1/1,000 or 1/20,000 mg. of the dried alcoholic extract of muscle or platelets forms thrombin capable of coagulating 0.5 c.c. of oxalate plasma.

Bordet and Delange entirely separate the two phases of coagulation. The first phase consists in the formation of thrombin by the interaction of serozyme and cytozyme in an ionized calcium medium. The solution of sodium oxalate precipitates the calcium salt in the plasma and thus causes the decalcification of the mediums. The coagulation is produced by the action of the thrombin formed in the first phase on the plasma (fibrinogen) added at the same time as the sodium oxalate solution (second phase). The separation of the two phases allows one to measure the quantity of thrombin formed in a given unit of time. The more thrombin there is in the solution, the quicker is the coagulation. Another advantage of their method consists in the employment of relatively pure solution. They take the blood in a paraffined tube containing a solution of sodium oxalate. The blood remains liquid, and after prolonged and speedy centrifugalization furnishes a plasma that is almost free from cytozyme. By recalcification the plasma is coagulated, and after the clot is expressed one obtains a serum rich in serozyme containing only traces of cytozyme. For cytozyme, Bordet and Delange use an extract of platelets or of organs, pure and sufficiently concentrated. To determine the strength of a substance in cytozyme, one proceeds in the following manner: The solution is treated with serozyme in calcified solution for fifteen minutes. Then the oxalate plasma is added. The time which elapses between the addition of the plasma and the beginning of the coagulation is inversely proportional to the amount of thrombin formed. If the plasma remains liquid, one concludes that the medium contains no thrombin.

Hirschfeld and Klinger have noticed the affinity of the cytozyme for the globulin of serum. The important rôle played by the globulins in most serologic reactions is a familiar fact. These findings have led them to inquire whether the technic of coagulation would not allow

them to discover certain phenomena of immunity. They have accordingly directed their attention especially toward a possible deviation of the cytozyme analogous to the deviation of the complement in the Wassermann reaction.

THE COAGULATION TEST

This reaction is based on the fact that the organ extracts employed in the Wassermann reaction represent very active cytozyme. This property of the cytozyme disappears after contact with a syphilitic serum, while it remains intact after a similar treatment with a normal serum.

In short, one measures the activity of a certain quantity of an extract after mixing it with a serum to be examined. If coagulation is not retarded sensibly and the extract is active in its coagulating power, the serum is normal. If, on the other hand, the coagulation is feeble or completely inhibited, the serum is syphilitic.

DIRECTIONS FOR THE REACTION

1. For serozyme, Bordet and Delange employed the serum of rabbit. Hirschfeld and Klinger have found that sheep's or goat's blood is richer in serozyme than that of the rabbit. These animals have less delicate platelets. They consider that paraffined tubes for receiving blood are not essential, if these vessels are perfectly clean and dry, warmed to 40 C. and the blood is drawn by a cannula. The latter authors have found beef blood unsuitable and we have likewise. We prefer paraffined vessels.

PREPARATION OF SEROZYNE

A 300-c.c. flask is filled with 100 c.c. of water and marked accurately at the fluid level. The flask is sterilized with dry heat to 180 C. for half an hour and then coated all over with paraffin. One puts into the flask 10 c.c. of the 1 per cent. sodium oxalate solution and 0.5 c.c. of 10 per cent. sodium chlorid solution for each 100 c.c. of blood. Mix them well by shaking. Fill with blood to the desired mark and shake it gently but thoroughly. Pour the blood thus prepared into centrifuge tubes heated to 40 C., and speedily centrifugalize it till the cellular elements have settled to the lower half of the tube. Remove the clear plasma with a pipet, taking care not to remove the red cells at the same time. Centrifugalize the clear plasma for a second time for at least thirty minutes to further get rid of the cytozyme present. Plasma thus obtained can be stored for three days in a refrigerator. It should be clear, yellowish in color and free from hemoglobin. This is the oxalate plasma.

FOR SEROZYME OR EXTRACT OF SERUM

To 10 c.c. of the oxalate plasma thus obtained, add 1.2 c.c. of the 1 per cent. calcium chlorid solution. Place the mixture in incubator until the clot is firmly formed. Express the clot by means of a pair of broad sterilized forceps. Sometimes it is necessary to repeat the procedure if not entirely clear. Then leave the clear liquid in the incubator for another half hour to destroy the further formation of thrombin. It is well to prepare the serozyme four or five hours before the experiment. Before use, the serozyme thus obtained should be diluted to five times its volume with 0.85 per cent. sodium chlorid, and the mixture should stand for one hour.

2. Calcified saline is prepared by mixing 100 c.c. of 0.85 per cent. of sodium chlorid and 5 c.c. of 1 per cent. solution of calcium chlorid. Fränkel and Thiele recommended 5 per cent. calcium chlorid in physiologic salt solution. We have tried their suggestion and find it does not work. Moreover, it is physiologically impossible, for it is a well-known fact that in strengths above 0.5 per cent. calcium solution clotting is impossible.

3. Oxalate plasma is prepared in the proportions given in Table 1.

TABLE 1.—Preparation of Oxalate Plasma

Oxalate plasma	20 parts
Solution sodium oxalate, 1 per cent.	20 parts
Normal saline	60 parts

This mixture should be prepared just before use.

4. For the organ extract, all alcoholic extracts may be used. Merck's preparation of guinea-pig's heart extract, of which 0.1 c.c. of a dilution of 1 : 160 causes coagulation after contact with serozyme in three to four minutes, is recommended by Hirschfeld and Klinger. We have prepared even better extracts of our own, both from guinea-pig and from human hearts.

TITRATION OF EXTRACTS

In order to ascertain what doses should be used in the experiment, there is prepared a series of dilutions of extract in 0.85 per cent. sodium chlorid solution, doubling each time the quantity of sodium chlorid solution. We recommend the initial dilution of 1 : 10 strength, to be followed consecutively by 1 : 20, 1 : 40, 1 : 80, 1 : 160 and 1 : 240. Mix 0.1 c.c. of each dilution with 1 c.c. of calcified saline and 0.5 c.c. of serozyme diluted one hour before. Let the mixture stand at room temperature for fifteen minutes, and add to it the mixture of oxalate plasma. One selects for the reaction the three consecutive dilutions, of which the first and second coagulate the plasma in from one to two minutes, and the third in from three to four minutes.

PREPARATION OF PATIENT'S SERUMS

In taking patient's blood, great care should be exercised to avoid hemolysis in the specimens to be tested. All serums should be inactivated at 58 C. for one hour in order to destroy the cytozyme present in them.

TECHNIC OF THE TEST

It is necessary to state that in order to make the test of diagnostic value, every detail is to be carried out accurately. We refer to the collecting of blood from the animals for experiments. The measurement must be carefully made in the quantity of blood taken and in the reagents used. The time for incubation of serozyme must be exact, and after the process it must be perfectly free from thrombin. Many a time, disappointment invariably follows only a slight overlooking of these seemingly little things. In every reaction, a preliminary titration of extract and control must be carried out before the main reaction is begun. It will be of great help if a preliminary test of one known positive and one known negative is also made. If the titration of extract fails to give a good result — either too rapid or too slow in the coagulation time — correct the fault at once before proceeding to the test proper.

TABLE 2.—Schema of Reaction

Patient's serum, 0.1 c.c.; heart antigen, 0.1 c.c.
Stand for one hour.
Calcified NaCl, 1.0 c.c.
Serozyme diluted, 0.5 c.c.

Stand for fifteen minutes.

Diluted oxalate plasma, 1.0 c.c.

After the addition of oxalate plasma, observe and record the time of coagulation. With a little practice, a large number of these specimens can be read at one time without difficulty.

THE CONTROLS

In order to make sure that the test is properly carried out, a series of controls must be made as follows:

The serozyme control consists of a mixture of diluted serozyme (1:5), 0.5 c.c., and calcified saline, 1 c.c. It should remain perfectly clear and liquid for hours, and show no signs of thrombin formation. This test should precede all others in the reaction.

The serum control (D) is to be carried out at the same time as the test proper with each patient's serum. It contains all the reagents except the extract, and it should remain liquid for at least three hours; it should not coagulate before the reading of all the specimens is completed.

TABLE 3.—REACTION AS USED BY HIRSCHFELD AND KLINGER AND IN OUR LABORATORY, SHOWING A SET OF EXPERIMENTS

	Patient	1:40 Minutes	Dilution of Extract 1:80 Minutes	1:160 Minutes	Serum Without Extract	Result of Test	Wassermann Result
1	Surgical	5	8	10	0	—	—
2	Surgical	5	8	10	0	—	—
3	Latent syphilis	8	0	0	0	++	++
4	Interstitial keratitis	9	0	0	0	++	++
5	Lesion on penis, ulcer mollis	5	8	10	0	—	—
6	Latent syphilis	8	0	0	0	++	±
7	Cerebrospinal syphilis (spinal fluid)	8	18†	40†	0	+	—
8	Gastritis	6	8	10	0	—	—
9	Asthma	5	8	11	0	—	—
10	Secondary anemia	5	8	10	0	—	—
11	Influenza	5	8	10	0	—	—
12	Latent syphilis (spinal fluid)	8	15	0	0	++	++
13	Cerebrospinal syphilis (spinal fluid)	10	0	0	0	++	++
14	Cerebrospinal syphilis (spinal fluid)	10	0	0	0	++	++
15	Known positive	7	0	0	0	++	++
16	Known negative‡	4	6	8	0	—	—

*The figures indicate the time necessary for coagulation; 0 = no coagulation after four hours. The extract controls alone coagulated in one, two and three minutes, respectively.

†Feeble.

‡Serozyme alone, 0.

The plasma control is to be carried out separately and before the main test is begun. It consists of a mixture of 1 c.c. of calcified saline, and 0.5 c.c. of serozyme diluted with 1 c.c. of diluted oxalate plasma. This mixture should remain in solution indefinitely.

Observe and record the time of coagulation.

After the adding of the oxalate plasma to all the tubes, the contents which are at first colorless and clear become flocculent and cloudy. The negative specimens starting from the first tubes gradually become thickened, gelatinous in consistency, and the coagulation takes place consecutively in from three to ten minutes in all the three tubes. The positive cases, however, remain either unclotted for hours in all the tubes or they very feebly and slowly coagulate. The time taken from reading is only of comparative value. There is no absolute standard of the coagulation time. It depends largely on the integrity of the serozyme, the strength of the cytozyme and the condition of the oxalate plasma. One reads, therefore, perhaps from two to eight minutes in one reaction and from ten to twenty-five in another. After a little practice one can judge accurately whether the given specimen is positive or negative by the character of the contents of the tubes. It is to be stated here that serozyme loses much of its power of thrombin formation after twenty-four hours' standing. Whenever possible it should be prepared anew.

COMMENT ON THE TEST

It is difficult to offer an explanation of the reaction. It is not primarily an anticoagulability of the syphilitic serum, because it affects its action only after contact with the organ extract. According to Hirschfeld and Klinger, in their early researches on the globulin of serum, there is a colloidal transformation of serum—a sort of ultramicroscopic precipitation of globulins due to contact with alcoholic extracts. This alteration of globulins probably effects absorption and diminution of the activity of the extract. This phenomenon is also observed, although in a less noticeable manner, with the cytozyme contained normally in the serum. One notices this with some syphilitic serums very rich in cytozyme which coagulate more rapidly in the control tubes and which do not furnish a sure result in the coagulation reaction. In such cases, the coagulation takes place very rapidly (in from two to five minutes) in the control tubes (D), while tubes with increasing doses of extract show retardation more marked in those that contain larger doses of extract. On the contrary a nonsyphilitic serum, rich in cytozyme, shows a coagulation more rapid in tubes containing the extract; while the control is slower, although it finally coagulates.

Hirschfeld and Klinger have found this test superior to the Wassermann in many instances, especially in cases of treated syphilis. Moreover, they have produced positive reaction to the Wassermann test by treating normal serums with emulsions of agar or of microbes, and also by prolonged agitation of diluted normal serums, whereas the coagulation test remained negative.

Their results show that the coagulation test for syphilis is as characteristic as the Wassermann.

An aqueous extract (cytozyme), Hirschfeld and Klinger find, has no effect on syphilitic serums. It is evident that the special change which the lipoid extract undergoes with the syphilitic serum cannot be due to anticytozyme, but that the reaction of the syphilitic serum with the lipoid extract leads to absorption of its coagulating powers, as a result of which it (lipoid extract) is less useful as cytozyme, or is even changed in its physical and chemical character.

COMPARISON WITH THE WASSERMANN REACTION

Of the 548 cases tested by us, fifty-one specimens are spinal fluids from different individuals. The classification given in Table 4 shows the number of the different diseases examined.

TABLE 4.—CLASSIFICATION OF CASES

Diseases	No.
Infectious diseases, including fevers, pneumonia, rheumatism, arthritis, tonsillitis, etc.	15
Congenital syphilis	5
Cerebrospinal syphilis	17
Primary syphilis	23
Secondary syphilis	32
Tertiary syphilis	68
Latent syphilis	84
Treated syphilis	73
General paresis, psychoses, etc.	5
Tabes dorsalis	6
Gummas	4
Skin diseases, including acne vulgaris, rosacea, etc.	37
Medical cases, including diabetes, anemia, diseases of the respiratory, circulatory and digestive systems, etc.	131
Surgical cases	48
Total	548

As all the tests have been run parallel with the Wassermann, comments will be made only on the cases giving different results—either positive with this test and negative with the Wassermann, or vice versa. We employ the original Wassermann technic, using four different antigens for each serum. We use alcoholic human heart antigens reenforced with cholesterin.

Of the 548 cases of blood and spinal fluid examined, fifty-eight cases, or 10.5 per cent., give positive results with the coagulation test and negative results with the Wassermann. The diseases comprising these fifty-eight cases are given in Table 5.

TABLE 5.—CASES IN WHICH THE COAGULATION TEST GAVE POSITIVE RESULTS AND THE WASSERMANN NEGATIVE

Latent syphilis	19
Treated syphilis	15
Secondary syphilis (spinal fluids)	2
Tertiary syphilis	11
Primary syphilis	4
Cerebrospinal syphilis	3
General paresis	2
Tabes dorsalis	1
Hodgkin's disease	1
Total	58

It is evident from these figures that the coagulation test is more delicate than the Wassermann. In our series it detects 10.5 per cent. more cases of syphilis than the Wassermann. In the latent and treated cases of syphilis, in which the Wassermann has often given negative results, the coagulation test has been positive. The four cases of primary syphilis in this series, in which infection was definite, and the lesions were characteristic of primary syphilis and persistent under local treatment, all gave negative results with the Wassermann, while the coagulation test was positive. Likewise in many tertiary cases the coagulation test was positive, while the Wassermann reaction was negative. In general paresis, tabes dorsalis and the cerebrospinal syphilis quoted above, there was, in most cases, not even a trace of complement deviation with the Wassermann reaction, while they came out positive with the coagulation test. There is one case of Hodgkin's disease not accounted for. On account of the lack of history, we are not able to comment on it.

It must be pointed out here that there are a few cases on our record having positive reaction with the coagulation test and negative with the Wassermann, and we cannot find any justification for such results from the history given. Repetition of the test with fresh reagents is of course highly advisable in these cases. The following cases are on record, and we have since had one or two others. In this, however, the test is probably as fallible as the Wassermann.

J. P., Hodgkin's disease, coagulation ++, Wassermann ±.
A. S., acne vulgaris, coagulation ++, Wassermann —.
L. W., pityriasis rosea, coagulation ++, Wassermann —.

On the other hand, it has been observed from time to time that a few serums react negatively with the coagulation test and positively with the Wassermann. Of the 548 cases, we have three specimens giving persistently negative results with this test and positive with the Wassermann. For example, we have:

B. A., syphilis, coagulation —, Wassermann ++.
L. B., spinal fluid, syphilis, coagulation —, Wassermann ++.
P., spinal fluid, syphilis, generalized eruption, coagulation —, Wassermann ++.

In general, we have found that hemolyzed specimens tend to produce coagulation in all the tubes, regardless of the presence or not of tissue extract.

We have so far tested only fifty-one specimens of spinal fluids from different patients. The results have been most gratifying. In quite a few cases the Wassermann has given negative results while the coagulation test has been positive: in fact, of the fifty-one cases, the coagulation test gives eleven more positive than the Wassermann, making a difference of 21 per cent. more positives for the coagulation test. The original publication reports unfavorable results with the spinal fluids tested. Our small experience, we believe, allows us to state that the spinal fluid, inactivated at 58 C. (136.4 F.) for half an hour and used in dose of 0.4 c.c., gives good results with this test.

The question arises as to the effect of the age of the serums on this coagulation test. We have tested about 150 serums of different ages and at different times. The time elapsed has been from two weeks to two months in different series of the specimens. The results have been uniformly good. With the exception of specimens showing deterioration, they all stand well for at least four weeks, if kept on ice. When a serum deteriorates, it generally gives a positive reaction. It is safe, therefore, to make a conservative estimate that all serums which have been inactivated at 58 C. for one hour can be kept in an ice chest for one week or possibly more without the reaction being affected.

For the purpose of studying the stability of the antibodies in the serum, we have made the following experiments: We have heated a few specimens of serums to 65 C. (149 F.) for from three quarters of an hour to an hour without generally altering the reaction. A few specimens heated to 70 C. (158 F.) or over showed a tendency of the negative specimens to become positive.

While the results are encouraging with our work for the past nine months, we would still recommend that all the tests should be done hand in hand with the Wassermann. This is especially important with those who have had little or no experience in serologic work. In the hands of experienced workers, this is unquestionably a more delicate test than the Wassermann, and only further work can show us its scope and limitations.

CONCLUSIONS

1. The coagulation test carried out by thoroughly reliable and conscientious workers is quite as specific as, and more delicate than the Wassermann, in cases of treated, latent and cerebrospinal syphilis.

2. Syphilitic cases, after prolonged and effective treatment, give negative results with the coagulation test, as with the Wassermann.

3. A few primary cases have given a positive result with the coagulation test, while the Wassermann was still negative.

4. Spinal fluids, after inactivation for half an hour at 58 C., give good results with the coagulation test, if used in doses of 0.4 c.c.

Our deepest gratitude is due to Prof. G. N. Stewart for his valuable suggestions and advice in carrying out this work.

2047 East Ninth Street.

BIBLIOGRAPHY

Bordet, J., and Delange, J.: Ann. de l'Inst. Pasteur, 1912, xxvi, 657, 737; ibid., 1913, xxvii, 341.

Fränkel E., and Thiele, F.: München. med. Wchnschr., 1914, lxi, 2095.

Hirschfeld, L., and Klinger, R.: Deutsch. med. Wchnschr., 1914, xl, 1607; Sem. méd., 1913, xxxiv, 361.

BOOK REVIEWS

A Textbook of Pathology. For Students of Medicine. By J. George Adami, M.A., M.D., LL.D., F.R.S., Professor of Pathology in McGill University, Montreal, and John McCrae, M.D., M.R.C.P. (London), Lecturer in Pathology and Clinical Medicine in McGill University, formerly Professor of Pathology in the University of Vermont. Second edition, enlarged and thoroughly revised. Octavo, 878 pages, with 395 engravings and 13 colored plates. Cloth, $5.00, net. Lea & Febiger, Publishers, Philadelphia and New York, 1914.

It is extremely difficult to arrive at a just estimate of the value of this book. The authors state that, while it is not by any means an abbreviation of Professor Adami's Principles of Pathology, it almost necessarily follows the same general lines of presentation. All who, like the reviewer, read with almost the charm of a novel the author's delightful presentation of general pathology in the first volume of the larger work, will be prepared for the same clear and interesting handling of the large underlying problems of disease. In this they will not be disappointed. They will also remember that the second volume of the previous work revealed by its contrast the predominant interest of the author. The facts of pathological anatomy and histology have not fared better in the present work. In their preface the authors state that "the reader will find that continued emphasis is placed on the reasons underlying pathological conditions; although we trust the facts themselves have not been neglected." After a careful reading of the entire book, the reviewer is forced to the conclusion that their hope has not been fulfilled. Of the 810 pages of text, 399 are devoted to General Pathology, and under "Special and Systemic Pathology" in Part Two, about one-third of the discussion is occupied with physiology, normal and pathological. At the most, one-third of the book, or less than 300 pages, is left for the facts of special pathological anatomy. Such a standard textbook as Ziegler's gives more than one half of its nearly 2000 pages to this aspect of pathology. One must admit that pathology includes the whole of our knowledge of disease, and that our understanding of pathological processes has been vastly widened by the application of physiological and chemical methods to their elucidation. One must also admit that investigations of the causes of disease, especially by bacteriological methods, and of the mechanism of the body's defense against infection, have made strides of late years, which a textbook should reflect. Clinical medicine is also contributing much toward an adequate pathology of the living. Pathological anatomist, physiologist, chemist, bacteriologist, and clinician are all concerned with the same problem, each approaching it from a special point of view and attempting a solution of it by special methods. Pathology includes them all. But this is a textbook intended for students, and in our education of the student it has always been the custom to draw the lines which separate the different avenues of approach to knowledge more sharply than the overlapping of their boundaries might seem to warrant. The reviewer cannot look forward to the time when pathological anatomy will be an outworn science. It will always be necessary for the physician, as Virchow emphasized, to think anatomically. If the pathologist does not teach him to do so, who shall? If "the reasons underlying pathological conditions" were selfevidencing and inescapable, like the deductions of mathematics, then the facts might conceivably be omitted. In the present state of pathology, however, much difference of opinion exists as to these reasons, and a satisfactory presentation of all of the arguments requires, first of all, the clear statement of every one of the facts from which men draw such varying conclusions. Medical students have an inborn preference for theoretical discussion, and a wholly natural aversion to the acquisition

of mere dull facts, and the reviewer feels strongly that this book will fall in quite too well with these natural predilections. Certainly no one can turn to it for detailed and authoritative statements of the known facts about the lesions of disease in any portion of the body. On the other hand, the general discussions of principles are admirable, and calculated both to interest the student and to stimulate him to think. If the book had been entitled An Introduction to Clinical Medicine it would have given a much clearer idea of its scope, but on page 187 the authors state that "this is neither a textbook of bacteriology nor a work on clinical medicine." This sentence suggests that they had a lurking fear lest their readers might so construe the book. On page 544 they seem almost to apologize for intruding such tiresome details as pathological histology. In discussing lobar pneumonia, they write "To understand properly how this changes to the so-called *gray hepatization*, a consideration of the microscopic appearance is necessary."

Certain criticisms in detail are called for. There are many obvious errors due to bad proof-reading, the worst of which are in the Table of Contents of Chapter Two, which does not follow the subsequent divisions in the text and contains such a slip as "Disturbances of the intestinal secretions" for "internal secretions." The discussion of the action of poisons, pages 71 to 75, is very inadequate. Either it should have been omitted, and the reader referred to books on pharmacology, or some notice should have been taken of the existence of the vegetative nervous system, and present knowledge of the pharmacodynamic action of drugs on it. Adrenalin and barium chlorid are put down as drugs acting alike on the unstriped muscle of the vessels. Throughout the discussions, both of immunity and of the internal secretions, a strong impression is created that hypotheses are in the same category with facts. On page 99 the reader is given to understand that an actual hormone has been isolated from the pancreas, which has definitely known functions in connection with the carbohydrate metabolism, and absence of which explains pancreatic diabetes. On page 162 is the following more remarkable statement, "Nor must it be thought that complement and amboceptor are merely theoretical names, for each has a definite existence, and is as real as if it were a chemical enclosed in a bottle and visible to the eye." Certainly the authors' conception of reality must differ from that of the reviewer, and probably from that of their colleague in the chair of chemistry. No sentence in the book more clearly indicates its most serious defects — the confusion of explanation with fact. It is not necessary to adduce other instances. Statements either wholly inadequate or misleading are made with reference to the relation of acidosis to diabetic gangrene; about eosinophilia in whooping cough on page 148, lymphocytosis being correctly given on page 447; as to the cause of death in anaphylactic shock, and concerning paroxysmal hemoglobinuria, and pathological polycythemia. Chronic lymphatic leukemia is not mentioned in the text, though a color plate of it is copied from Cabot; nor is hemolytic family jaundice described.

The discussion of cirrhosis of the liver is excellent. It is a pleasure to find a pathologist saying frankly that he has never seen a true Hanot cirrhosis, and that this must be very rare in North America. On the other hand, the discussion of nephritis seems to the reviewer very incomplete, and to perpetuate an indefensible nomenclature in the light of present knowledge of the detailed lesions of the kidney and their mode of development. This criticism is made with full recognition of the large legitimate difference of opinion which may still exist in this field.

A final criticism applies to almost all students' textbooks in the English language. No hint is given of the historical development of our knowledge of pathology, and the book contains but one bibliographic reference. Frequent mention is made of the work of younger American and English investigators, while the great names which mark epochs in the growth of the science are nowhere mentioned. The student would never know that Virchow or Ribbert

or Cohnheim had lived, or done anything to elucidate inflammation, or thrombosis and embolism, while he was quite familiar with Fischer's theories of edema and Klotz's unconfirmed experiments on arteriosclerosis. Syphilitic mesaortitis seems to have gotten itself described without the help of Heller and Döhle, while the reader is told where to find Lewis' and Mackenzie's work on the cardiac arrhythmias — the one reference in a textbook, not of clinical medicine, but of pathology. One would suppose that pathological anatomy was as old as the Euclidean geometry, and the sources of our knowledge as obscure. One cannot be surprised that the American medical student has so little historical perspective and so little respect for thorough scholarship when one reads his textbooks. The illustrations are, for the most part, unsatisfactory, a failing which must be laid at the door of American publishers rather than of their authors.

With all this criticism, the reviewer would testify to the interest with which he followed the elucidation of the many complex influences which the pathologist must reckon with today in his study of disease and its causes. The book is a readable, highly suggestive work, valuable for any student before entering on his clinical years, if supplemented by a thorough course of instruction in pathological anatomy and histology.